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PSYCHOPHARMACOLOGY ABSTRACTS

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ABSTRACTS

PRECLINICAL PSYCHOPHARMACOLOGY

01 CHEMICAL SYNTHESIS, ISOLATION AND CHARACTERIZATION

38489
AUTHORS: Jacobson, Arthur E.; Mokotoff, Michael.
TITLE: Azabicyclo chemistry. I. Synthesis of 1,5-methano-7-methoxy-2,3,4,5-tetrahydro-1H-2-benzazepines. B-norbenzomorphans.
SOURCE: Journal of Medicinal Chemistry.
SOURCEID: 13(1):7-9, 1970.

Using 5-methoxyindan-1-one-3-acetic acid as starting material, 1,5-methano-7-methoxy-2,3,4,5-tetrahydro-1H-2-benzazepine and its N-methyl derivative, 1,5-methano-7-methoxy-2-methyl-2,3,4,5-tetrahydro-1H-2-benzazepine hydrochloride were synthesized via an oxime which was converted to an amino acid. Cyclization to a lactam was effected by carbodiimides, the lactam then being reduced to 2,5-methano-7-methoxy-2,3,4,5-tetrahydro-1H-2-benzazepine hydrochloride (compound 10), with subsequent N-methylation (compound 11). The analgesic activity of compound 10 was half that of codeine, while that of compound 11 was comparable to that of codeine. 13 references.

46395
AUTHORS: Curry, A. S.; Patterson, D. A.
TITLE: A procedure for the analysis of illicit diamorphine samples.
SOURCE: Journal of Pharmacy and Pharmacology (London).
SOURCEID: 22(3):198-201, 1970.

A procedure for the analysis of illicit diamorphine samples is outlined; it consists of preliminary examination of the material by infrared spectrophotometry, followed by thin layer and gas liquid chromatography. Data are recorded for 18 likely contaminants. 9 references. (author abstract modified)

41907
AUTHORS: Ho, Beng, T.; Tansey, L. Wayne; Balster, Robert L.; An, Rong; McIsaac, William M.; Harris, Robert T.
TITLE: Amphetamine analogs. II. Methylated phenethylamines.
SOURCE: Journal of Medicinal Chemistry.
SOURCEID: 13(1):134-135, 1970.

The purpose of this study was to determine the effect of amphetamine analogs on pentobarbital induced sleeping time in mice. The results of the conditional behavior are expressed as ED50 and presented in a table. The analogs involved in the experiment were: (1) 2,5-dimethoxy-4-methylamphetamine (DOM), (2) 2,5-dimethoxy-N,4-dimethylamphetamine, (3) mescaline, (4) 2,5-dimethoxy-4-methyl-beta-phenethylamine, (5) 2,5-dimethoxy-N,4-dimethyl-beta-phenethylamine, and (6) 2,5-dimethoxy-N,N,4-trimethyl-beta-phenethylamine. Compounds which were the most active in disrupting rat behavior were 1 and 4. Although the latter had 3/4 the activity of 1, it is 5 times more potent than mescaline. N-Methylation of both the phenethylamine and phenylisopropylamine series resulted in compounds much less effective in behavioral disruption. A 5 fold loss in activity was observed from 1 to 2, and a 7.5 fold loss from 4 to 5. Among compounds 2, 4, 5, and 6, both 4 and 5 were found to potentiate the sleeping time. A 4 fold difference in toxicity was observed between 3 and 4. 4 references.

41973
AUTHORS: Boakes, R. J.; Bradley, P. B.; Briggs, I.; Dray, A.
TITLE: Effects of lysergic acid derivatives on 5-hydroxytryptamine excitation of brain stem neurones.
SOURCE: British Journal of Pharmacology (London).
SOURCEID: 38(2):453P-454P, 1970.

The interactions of d-lysergic acid diethylamide (LSD-25), 2-bromo-lysergic acid diethylamide (BOL), and methysergide with the effects of 5-hydroxytryptamine (5-HT) and of other compounds which stimulate or depress neuronal activity were studied. LSD-25, applied iontophoretically for periods of 5 mins. or more at currents of 50nA, consistently blocked or depressed excitatory responses to 5-HT but not those to acetylcholine, (-)-norepinephrine, or (+/-)-homocysteic acid. LSD-25 did antagonize the excitatory effects of glutamate ions on neurons which could be excitated by 5-HT, but not on neurons which could be inhibited by 5-HT. Inhibitory responses to 5-HT, acetylcholine, (-)-norepinephrine, glycine and gamma-aminobutyrate were never affected by LSD-25. BOL, applied in the same way as LSD-25, only rarely showed antagonism to 5-HT excitation and to glutamate excitation of neurons which could be excited by 5-HT. Methysergide antagonized 5-HT and glutamate excitation more frequently than BOL, but less frequently than LSD-25. LSD-25 therefore appears to be an effective antagonist of 5-HT excitation of neurons in the cat brain stem. Of the 2 analogs of LSD-25 tested, BOL, which was relatively ineffective, is not known to possess any psychotomimetic activity, while methysergide which showed some activity, has been reported to be hallucinogenic. A tentative correlation between hallucinogenic activity and antagonism to 5-HT excitation in brain stem is suggested. 3 references.

46397
AUTHORS: Ebadi, Manuchair S.
TITLE: Increase in brain pyridoxal phosphate by chlorpromazine.
SOURCE: Pharmacology (Basel).
SOURCEID: 3(2):97-106, 1970.

Male Sprague-Dawley rats were administered chlorpromazine hydrochloride and trifluoperazine hydrochloride subcutaneously in doses of 15mg/kg, and in doses of 7.5mg/kg, in an experiment involving brain pyridoxal phosphate. It was found that

chlorpromazine increased the level of pyridoxal phosphate in the brain and the activity of pyridoxine phosphate oxidase. Actinomycin D or cycloheximide blocked the increase in the activity of the oxidase. Discussed is the possibility of coenzyme induced activation of dopa decarboxylase and a subsequent increase in the turnover rate of dopamine. 47 references.

40126
AUTHORS: Breese, G. R.; Kopin, I. J.; Weise, Virginia K.
TITLE: Effects of amphetamine derivatives on brain dopamine and noradrenaline.
SOURCE: British Journal of Pharmacology (London).
SOURCEID: 38(3):537-545, 1970.

A study was made of the effects of amphetamine derivatives on brain dopamine and norepinephrine. The compounds were dissolved in Elliott's "B" solution and injected intracisternally into Sprague-Dawley rats weighing 180 to 200 gm; a total volume of 20mcl was injected. At various times after injection of the drugs, the animals werekilled by cervical fracture and decapitated. The brains were removed, rinsed in cold water, homogenized in 10 ml of ice cold 0.4 N perchloric acid and kept frozen until analyzed. Metaraminol, alpha-methyl-octopamine, alpha-methyl-m-tyramine, and alpha-methyl tyramine lowered brain norepinephrine without having an effect on brain dopamine. Amphetamine, mephentermine, and norephedrine had no effect on brain catecholamines after intracisternal injection. There was no reduction in brain dopamine content after intracisternal injection of alpha-methyl-m-tyramine, yet the resulting brain concentration of alpha-methyl-m-tyramine was several times higher than after intraperitoneal injection of alpha-methyl-m-tyrosine, which decreased brain dopamine. The decreased synthesis of labeled catecholamines from labeled tyrosine after alpha-methyl-m-tyrosine suggested that this compound inhibits tyrosine hydroxylase in addition to its action of displacing brain amines. 26 references.

40241
AUTHORS: Miller, P. P.; Cox, R. H., Jr.; Snodgrass, W. R.; Maickel, R. P.
TITLE: Comparative effects of p-chlorophenylalanine, p-chloroamphetamine and p-chloro-N-methylamphetamine on rat brain norepinephrine, serotonin and 5-hydroxyindole-3-acetic acid.
SOURCE: Biochemical Pharmacology (Oxford).
SOURCEID: 19(2):435-442, 1970.

Comparative time course effects of p-chlorophenylalanine (PCPA), p-chloroamphetamine (PCA), and p-chloro-N-methylamphetamine (PCMA) on rat brain norepinephrine (NE), serotonin (5-HT) and 5-hydroxyindole-3-acetic acid (5-HIAA) are reported. The levels of 5-HT, 5-HIAA, and NE were determined in single brain areas by a modification of the method of Maickel et al. Effects of PCPA, PCA, and PCMA on levels of 5-HT, 5-HIAA, and NE in discrete areas of rat brain are discussed and presented in tabular form. The time course of effects of a single dose of PCPA on rat brain amines shows a significant lowering of 5-HT and 5-HIAA, beginning on day 1 and lasting for about 8 days. In most brain areas, levels of norepinephrine are also lowered significantly on days 1 through 5. In contrast, both PCA and PCMA decrease brain 5-HT and 5-HIAA, beginning 2 to 4 hours after dosage and continuing for more than 4 days, with no depleting effect on brain NE. 14 references.

40242
AUTHORS: Yoo, C. S.; Lee, Woo Choo.
TITLE: Blockade of the cardiac action of phenylephrine by bretylium or cocaine.
SOURCE: Journal of Pharmacology and Experimental Therapeutics.
SOURCEID: 172(2):274-281, 1970.

Blockade of the cardiac action of phenylephrine by bretylium or cocaine was studied. The effect of bretylium or cocaine on the positive inotropic action of phenylephrine was investigated on isolated atria from rabbits. The tissue concentration of catecholamines was determined by the spectrophotofluorometric procedure of Shore and Olin. In atria in which catecholamines had

been almost completely depleted by reserpine, phenylephrine exerted a positive inotropic action which was not significantly different from that observed on normal atria. Bretylium or cocaine blocked the cardiostimulant action of phenylephrine on atria from normal rabbits but had no blocking action on atria depleted of catecholamines by reserpine. After replenishment of the depleted catecholamines by exposing the atria to norepinephrine, the blocking effect of the cardiac action of phenylephrine by bretylium or cocaine was restored. It was shown that the less the reduction in myocardial catecholamines, the greater the depression of the action of phenylephrine by bretylium or cocaine. It is suggested that bretylium or cocaine may combine with the catecholamine molecule and interfere with the action of phenylephrine at the adrenergic receptor. 15 references. (author abstract modified)

40243
AUTHORS: Urquilla, Pedro R.; Stitzel, Robert E.; Fleming, William W.
TITLE: The antagonism of phentolamine against exogenously administered and endogenously released norepinephrine in rabbit aortic strips.
SOURCE: Journal of Pharmacology and Experimental Therapeutics.
SOURCEID: 172(2):310-319, 1970.

The antagonism of phentolamine against exogenously administered and endogenously released norepinephrine in rabbit aortic strips was studied. The adrenergic nerve terminals of the rabbit aorta are located at the medial adventitial border. Thus it is quite likely that the concentration of endogenously released norepinephrine progressively declines as it diffuses from the nerve terminals toward the lumen. In contrast, phentolamine is probably equally distributed throughout the smooth muscle. Under these circumstances, equilibrium competitive antagonism deviates from the usual kinetics of agonist -antagonist interactions. In rabbit aortic strips, phentolamine is a more effective antagonist of tyramine and nerve stimulation than it is of exogenously administered norepinephrine. At a concentration of 1.7X10-(7)M, phentolamine preferentially antagonizes the effects of endogenously released norepinephrine without affecting either the uptake of H(3)-norepinephrine and H(3)-tyramine or antagonizing the chronotropic effects of tyramine on rabbit atria. These results indicate that concentrations of phentolamine which effectively block alpha adrenergic receptors have no significant presynaptic effects. 33 references. (author abstract modified)

40244
AUTHORS: Kirpekar, S. M.; Prat, J. C.; Yamamoto, H.
TITLE: Effects of metabolic inhibitors on norepinephrine release from the perfused spleen of the cat.
SOURCE: Journal of Pharmacology and Experimental Therapeutics.
SOURCEID: 172(2):343-350, 1970.

The effects were studied of metabolic inhibitors on norepinephrine release from the perfused spleen of the cat. Norepinephrine (NE) was released from perfused cat spleens by either nerve stimulation or injection of potassium in phenoxybenzamine treated animals. Spontaneous release of NE was increased when spleens were perfused with nitrogenated glucose free Kreb's solution. Similarly, treatment with dinitrophenol with glucose deprivation also resulted in increased spontaneous release. Ouabain also increased it. Sulfhydryl group inhibitors, iodoacetic acid, p-chloro-mercuribenzoate, and N-ethylmaleimide markedly and irreversibly blocked release evoked both by nerve stimulation and potassium. Glucose deprivation or treatment with 2-deoxy-glucose did not affect release. Anoxia, dinitrophenol, and cyanide appeared to slightly enhance the release, at leastinitially, in response to nerve stimulation or potassium injection. Anoxia in absence of glucose for over two hours markedly inhibited release due to nerve stimulation or potassium. Dinitrophenol or cyanide in the absence of glucose produced similar inhibition. It is concluded that the energy requirements for the release of NE are not extensive, and that

release is not impaired in the absence of either oxidation or glycolytic metabolism. 23 references. (author abstract modified)

40245
AUTHORS: Farnebo, Lars-Ove; Hamberger, Bertil.
TITLE: Release of norepinephrine from isolated rat iris by field stimulation.
SOURCE: Journal of Pharmacology and Experimental Therapeutics.
SOURCEID: 172(2):332-341, 1970.

The field stimulation induced release of endogenous norepinephrine (studied by fluorescence histochemistry) and of exogenous H(3)-norepinephrine was investigated in the isolated rat iris. Isolated irides were incubated with H(3)-norepinephrine and then superfused with physiologic buffer before they were stimulated for 60 minutes. The stimulation caused a high release of H(3)-norepinephrine for 15 to 20 minutes, which then declined. A slight reduction of the fluorescence intensity in the adrenergic nerves was observed. No release of norepinephrine occurred when (Ca(++) was excluded from the buffer. Incubation with reserpine phosphate before the superfusion caused a high spontaneous tritium efflux, and this efflux was further enhanced by stimulation. These data confirm earlier in vivo findings that the depletion by reserpine can be influenced by nerve impulses. One hour after treatment with H44/68 (a potent inhibitor of tyrosine hydroxylase), a higher stimulus induced depletion of endogenous norepinephrine and a lower release of H(3)-norepinephrine was found, as compared to the release from irides of untreated rats. It may be that exogenous H(3)-norepinephrine is not available for stimulus induced release to the same extent after H44/68, or that the nerves attempt to save as much transmitter as possible. 28 references. (author abstract modified)

40246
AUTHORS: Zigmond, Michael J.; Wurtman, Richard J.
TITLE: Daily rhythm in the accumulation of brain catecholamines synthesized from circulating H3-tyrosine.
SOURCE: Journal of Pharmacology and Experimental Therapeutics.
SOURCEID: 172(2):416-422, 1970.

Daily rhythm in the accumulation of brain catecholamines synthesized from circulating H(3)-tyrosine was studied. An aliquot of supernatant fluid of centrifuged rat brain was assayed for tyrosine by the method of Waalkes and Udenfriend, and the data were analyzed by analysis of variance and by the Student's test. The accumulation of H(3)-catecholamines in brain was measured in rats given i.p. H(3)-tyrosine (H(3)-TYR). In animals injected at the same time of day, brain H(3)-TYR reached a peak within 10 minutes of injection and remained at this level for at least 120 minutes. Brain H(3)-catecholamine content was highest 60 minutes after injection. However, H(3)-catecholamine content corrected for the specific activity of H(3)-TYR during the accumulation period attained its peak within 10 minutes of the injection and remained at this level for the next 2 hours; this suggests that the newly synthesized catecholamine equilibrates rapidly with 1 of several brain pools. Animals maintained under light for 12 hrs./day received H(3)-TYR at the middle or end of the daily light or dark period and were killed after 3 or 60 minutes. The accumulation of H(3)-catecholamine was significantly higher in the middle of the light period than in the dark period when correction was made for fluctuations in the specific activity of tyrosine. 26 references. (author abstract modified)

40309
AUTHORS: Krauss, Kenneth R.; Kopin, Irwin J.; Weise, Virginia K.
TITLE: The effect of bretylium on amine retention in rat heart.
SOURCE: Journal of Pharmacology and Experimental Therapeutics.
SOURCEID: 172(2):282-288, 1970.

The effect of bretylium on amine retention in rat heart was studied. Bretylium, a compound which blocks release of norepinephrine from sympathetic nerve endings, has been found to deplete myocardial stores of metaraminol and several other false transmitters, but does not alter levels of cardiac norepinephrine or alpha-methylnorepinephrine. Bretylium is more effective than desmethylimipramine (desipramine) or cocaine in reducing metaraminol levels, although these drugs more effectively inhibit uptake of metaraminol. Since bretylium does not appear to displace amines at their binding sites or to accelerate metabolism of metaraminol, these results suggest that a drug membrane interaction other than inhibition of uptake is the basis for the release of these amines. The susceptibility to release appears to be inversely related to the affinity of the amines to binding sites within the neuron, and it is suggested that bretylium acts directly or indirectly to alter the rate of efflux of these amines from the neuronal cytoplasm. Unlabeled metaraminol was assayed by the method of Shore and Alpers; unlabeled norepinephrine was determined by a modification of the method of Anton and Sayre. 20 references. (author abstract modified)

40311
AUTHORS: Caldwell, H. William; Goldberg, Leon I.
TITLE: An evaluation of the vasodilation produced by mephentermine and certain other sympathomimetic amines.
SOURCE: Journal of Pharmacology and Experimental Therapeutics.
SOURCEID: 172(2):297-309, 1970.

An evaluation was made of the vasodilation produced by mephentermine and certain other sympathomimetic amines. Mephentermine injected into femoral, renal, or superior mesenteric arteries of pentobarbital anesthetized dogs increased blood flow in proportion to dose. The effect was not blocked by propranolol, atropine, or antihistamine compounds. Vasodilation was also observed with pseudoephedrine, d-amphetamine, methamphetamine, methyl phenidate, Lilly 390, and BW 654. No apparent relationship between structure and vasodilating activity was noted among these amines. Each of these amines also produced secondary vasoconstriction, particularly after phenoxybenzamine or reserpine. Segmental resistance studies in the perfused forelimb of phenoxybenzamine pretreated dogs showed that the decrease in total resistance produced by mephentermine is due to a reduction in small vessel resistance, as is the case with isoproterenol and glyceryl trinitrate. Mephentermine, unlike the other agents, increased resistance in the arterial segment. The demonstration of this vasodilation in these 3 vascular beds and relaxation of the isolated portal vein suggests that this dilating phenomenon is not selective as to vascular bed. 33 references. (author abstract modified)

40417
AUTHORS: Slotkin, Theodore; DiStefano, Victor.
TITLE: Urinary metabolites of harmine in the rat and their inhibition of monoamine oxidase.
SOURCE: Biochemical Pharmacology (Oxford).
SOURCEID: 19(1):125-131, 1970.

An investigation of the urinary metabolites of harmine hydrochloride administered intraperitoneally to Sprague-Dawley rats revealed the presence of harmol, harmol sulfate, and harmol glucuronide. No harmaline derivatives were found, indicating that although harmaline may be hydrogenated to harmine in vivo, hydrogenation of harmine to form harmaline does not occur. O-methylation which occurs in the metabolism of harmaline is observed with harmine, however. Of 5 radioactive fractions produced from the urine of rats treated with tritiated harmine hydrochloride, 1 was found to be a radioactive impurity in the injection solution. The remaining fractions contained metabolites in the percentages: V, 11%; IV, 2%; III, 69%; II, 18%. Each of the metabolites showed the capacity to inhibit monoamine oxidase. 13 references.

40418
AUTHORS: Aghajanian, G. K.; Foote, W. E.; Sheard, M. H.
TITLE: Action of psychotogenic drugs on single midbrain raphe neurons.
SOURCE: Journal of Pharmacology and Experimental Therapeutics.
SOURCEID: 171(2):178-187, 1970.

Because of the previous observation that d-lysergic acid diethylamide (LSD) inhibits raphe neurons, the possible effects on raphe units of other psychotogenic drugs were investigated. In addition to LSD, the following drugs were tested: 2-brom-LSD, N,N,-dimethyltryptamine, mescaline, 2,5-dimethoxy-4-methylamphetamine, scopolamine and atropine, phencyclidine, and various nonpsychotogens such as chlorpromazine. There were marked differences in the way the various psychotogenic drugs affected the activity of raphe units, depending on the structural class of the compounds administered. The drugs containing a N-methylated indolethylamine moiety (i.e., LSD, 2-brom-LSD, and N,N,-dimethyltryptamine) inhibited all raphe units, although 2-brom-LSD was usually not capable of producing total inhibition. The derivatives of phenethylamine or alpha-methyl-phenethylamine inhibited only those units located in the ventral portion of the dorsal raphe. Atropine, scopolamine and phencyclidine had no effect on raphe unit activity. None of the nonpsychotogenic compounds tested inhibited raphe activity. The results indicate that the indole and phenethylamine psychotogens have an overlapping, though not identical, effect on single units in the raphe nuclei, whereas the psychotogenic drugs which do not have the indole and phenethylamine structure do not affect raphe units. 43 references. (author abstract modified)

40572
AUTHORS: Cox, B.; Hecker, Sally E.; Weston, A. H.
TITLE: Effects of two cholinesterase inhibitors on acetylcholine release from the guinea-pig isolated ileum preparation.
SOURCE: Journal of Pharmacy and Pharmacology (London).
SOURCEID: 22(3):231-232, 1970.

The effects of 2 cholinesterase inhibitors on acetylcholine release from the guinea pig isolated ileum preparation were studied. Segments of ileum 3 to 4 cm long were suspended in 10 ml organ baths and exposed to NN'-di-isopropylphosphorodiamidic fluoride (mipafox) and to eserine. The release of acetylcholine from the ileum was high in the presence of eserine and low after treatment with mipafox. It is speculated that mipafox does not give complete protection to endogenously released acetylcholine. Both eserine and mipafox gave full protection to a standard dose of acetylcholine added to the bath. The results thus suggest that there must be differences between the hydrolysis of endogenous and exogenous acetylcholine by cholinesterase. 11 references.

40579
AUTHORS: Devoino, L. V.; Eremina, O. P.; Ilyutchenok, R. Yu.
TITLE: The role of the hypothalamo-pituitary system in the mechanism of action of reserpine and 5-hydroxytryptophan on antibody production.
SOURCE: Neuropharmacology (Oxford).
SOURCEID: 9(1):67-72, 1970.

The role of the hypothalamo - pituitary system in the mechanism of action of reserpine and 5-hydroxytryptophan (5-HTP) on antibody production was studied in hypophysectomized male chinchilla rabbits and in rabbits with lesions of the pituitary stalk. The inhibitory effects of 5-HTP and reserpine were abolished in both types of treated rabbits. Treatment of intact rabbits with reserpine and 5-HTP prolonged the latent period of the primary immune response and lowered the intensity of the primary and secondary immune responses. Since reserpine, serotonin and 5-HTP exert a similar effect on immune responses, it can be concluded that the inhibitory effect is exerted

through changes in the level of free serotonin. Reserpine, by preventing tissue binding of this biogenic amine, may produce a higher than normal content of free serotonin. The serotoninergic structures of the hypothalamus presumably participate in the mechanisms of action of reserpine and 5-HTP on the production of humoral antibody. 17 references. (author abstract modified)

40580
AUTHORS: Crawford, J. M.
TITLE: Anaesthetic agents and the chemical sensitivity of cortical neurones.
SOURCE: Neuropharmacology (Oxford).
SOURCEID: 9(1):31-46, 1970.

Anesthetics were administered systemically to decerebrate cats while recordings were made of the frequency of the spontaneous and drug induced firing of single pericruciate cortical neurons. An anesthetic produced essentially similar effects in a given cell on both the spontaneous synaptic firing and the responses to alternate microelectrophoretic ejection of acetylcholine and excitant amino acids. Barbiturates depressed the chemical sensitivity of cortical neurons in doses well below those necessary for surgical anesthesia, the duration of depression resembling the persistence of each agent in clinical practice. Subanesthetic doses of urethane were not very effective, but full anesthetic doses of chloralose markedly reduced chemical sensitivity of these cells for long periods. Low to moderate concentrations of nitrous oxide, trichlorethylene and halothane (bromochlorotrifluoroethane) had little direct effect on the firing of cortical neurons. The effects of higher concentrations of nitrous oxide on the cells were obscured by associated hyposica, but halothane levels exceeding 1.5%depressed excitability. Methoxyflurane seems remarkable in that it did not appreciably alter chemical sensitivity of cortical neurons, even at full anesthetic levels. None of the agents tested appeared to prevent depression of cortical neurons by GABA (gamma-aminobutyric acid). It is concluded that general anesthetics nonspecifically reduce the chemical excitability of cortical neurons, possibly by an action of postsynaptic membrane conductance changes. However, neurons in various regions of the nervous system appear to differ in their susceptibility to particular anesthetics. 47 references. (author abstract modified)

40582
AUTHORS: Robinson, Sumner M.; Milberg, Jane.
TITLE: Alterations of d-amphetamine sulfate lethality and body temperature in mice during acute altitude exposure.
SOURCE: Toxicology and Applied Pharmacology.
SOURCEID: 16(2):540-546, 1970.

Hyperthermia has been implicated in the toxicity of amphetamine in aggregated mice, as has acute exposure to simulated altitude (ALT), an environmental stress which lowers body temperature. Thermal responses to amphetamine are studied at ALT to determine whether elevated body temperatures would be similarly related to the lethal effects of this drug. Rectal temperatures after i.p. administration of d-amphetamine sulfate were monitored continually for 4 hours in isolated mice at sea level and an ALT of 19000 feet. At sea level, all doses of amphetamine resulted in hyperthermia; lethality occurred only with 75mg/kg, 100mg/kg and 125mg/kg with no fatalities at lower dosages. At ALT, the rectal temperatures of control mice were reduced 5 C within 1 hour. Increased lethality with amphetamine at ALT was apparent between 25mg/kg and 75mg/kg, while hypothermia was present at all dose levels although not as marked as with the controls. Hypothermia at ALT was least evident with 10mg/kg (2.5 C in 1 hour), a dose which had minimal effects on lethality. It would appear, therefore, that the hyperthermic effects of amphetamine were not associated with the increased lethality at altitude. 14 references. (author abstract modified)

40584
AUTHORS: Saunders, Robert N.; Miya, Tom S.; Bousquet, William F.
TITLE: Stimulation of DOPA-14C incorporation into melanoma tissue by chlorpromazine and reserpine.
SOURCE: Toxicology and Applied Pharmacology.
SOURCEID: 16(2):434-441, 1970.

Male mice bearing Harding-Passey melanomas were given i.p. injections of chlorpromazine or reserpine once daily for 7 days to determine the effect of the drugs on dopa-C(14) incorporation into melanoma tissue. On the 5th day of treatment, 1mcCi of dopa-C(14) (3.93 mCi/mM) was administered i.p. The mice were decapitated 72 hours after injection, and the tumors were excised and homogenized. The radioactivity in the melanosome containing fraction was measured by liquid scintillation procedures. Treatment with 5mg/kg chlorpromazine or 0.5mg/kg reserpine increased the specific activity of the melanosome containing fractions. The specific activity of the melanosome containing fractions from tumors in mice treated with 100mg/kg phenobarbital, 25mg/kg chlorpromazine sulfoxide, or 0.64mg/kg yohimbine did not differ from control values. The rate of in vitro conversion of dopa to melanin by tyrosinase present in the melanosome containing fraction was not influenced by chlorpromazine pretreatment or by the addition of 10(-4)M chlorpromazine to the reaction mixture. Apparent kinetic constants for tyrosinase isolated from chlorpromazine treated mice were identical with controls. 26 references. (author abstract modified)

40639
AUTHORS: Mayer, Susan E.; Southgate, P. J.; Wilson, A. B.
TITLE: Central nervous system stimulant action of fenfluramine in rabbits.
SOURCE: Journal of Pharmacy and Pharmacology (London).
SOURCEID: 22(3):239-240, 1970.

The central nervous system stimulant action of fenfluramine was studied in rabbits. After induction of deep sleep through administration of pentobarbitone, dexamphetamine sulfate (2mg/kg), fenfluramine hydrochloride (8mg/kg), and normal saline (1ml/kg) were injected intravenously. Both dexamphetamine and fenfluramine caused a rapid and complete electrocorticogram arousal, accompanied by body movement artefacts, widely dilated pupils, and intermittent masticatory movements. This alerting action of fenfluramine provides further evidence of its amphetaminelike stimulant properties. 8 references.

40671
AUTHORS: Beuthin, Patricia K.; Bousquet, William F.
TITLE: Long-term variation in basal and phenobarbital-stimulated oxidative drug metabolism in the rat.
SOURCE: Biochemical Pharmacology (London).
SOURCEID: 19(2):620-625, 1970.

A study was made of the long-term variation in basal and phenobarbital stimulated oxidative drug metabolism in the rat. Preliminary experiments were conducted to: determine whether the seasonal rhythmicity in oxidative drug metabolism is evident in the rat; determine if rhythmicity is present in the response of this species to enzyme stimulating drugs such as phenobarbital; and attempt a correlation of long-term alterations in drug metabolism with drug response measured under in vivo conditions. Experiments were carried out for 1 year from the 14th to the 17th of each month between 8 and 10 am. Hexobarbital sleeping times were measured at an ambient temperature of between 76 and 78 F. Male Holtzman rats weighing between 135 and 150 gm were challenged with hexobarbital sodium (100mg/kg) administered intraperitoneally 48 hrs, after receiving either saline (1ml/kg) or phenobarbital sodium (100mg/kg). The duration of loss of the righting reflex was measured. Other groups of rats which had received either saline or phenobarbital sodium were sacrificed and the livers prepared for enzyme assay.

Aminopyrine metabolism, p-nitroanisole metabolism, and hexobarbital metabolism were determined. The results suggest that the time of year may be an important variable in the evaluation of the enzyme stimulating properties of drugs and other foreign compounds. 18 references.

40750
AUTHORS: Lotti, Victor J.; Porter, Curt C.
TITLE: Potentiation and inhibition of some central actions of L(-)-dopa by decarboxylase inhibitors.
SOURCE: Journal of Pharmacology and Experimental Therapeutics.
SOURCEID: 172(2):406-415, 1970.

dl-Alpha-methyl-alpha-hydrazino-3,4-dihydrophenylpropionic acid (HMD) and N1-(dl-seryl)-N2-(2,3,4-trihydroxybenzyl)hydrazine (Ro-4-4602), 2 known inhibitors of aromatic amino acid decarboxylase (dopa carboxylase), were investigated for their effect on some centrally mediated actions of l-dopa. HMD enhanced the ability of l-dopa to increase motor activity in mice and rats and irritability in mice. In addition, HMD enhanced the reversal by l-dopa of reserpine induced hypothermia, suppression of locomotion and ptosis. Enhancement of the pharmacologic actions of l-dopa by HMD was associated with enhanced brain dopamine levels. In contrast, the vomiting response to l-dopa in dogs and pigeons was attenuated by treatment with HMD. Low doses of Ro-4-4602 (1-125mg/kg) potentiated l-dopa reversal of the locomotor suppressant and ptotic actions of reserpine, whereas high doses (125-625mg/kg) inhibited these actions of l-dopa. Carboxylase inhibitors can either inhibit or potentiate the central actions of l-dopa depending on whether they reach the brain sites where l-dopa acts. 12 references. (author abstract)e

40751
AUTHORS: Moore, Glynne E.; O'Donnell, Stella R.
TITLE: A potent beta-adrenoreceptor blocking drug: 4-(2-hydroxy-3-isopropylaminopropoxy)indole.
SOURCE: Journal of Pharmacy and Pharmacology (London).
SOURCEID: 22(3):180-188, 1970.

4-(2-Hydroxy-3-isopropylaminopropoxy)indole (LB46) is a competitive beta-adrenoreceptor blocking drug with a potency of between 4 and 7 times that of propranolol on the guinea pig isolated trachea and atria (chronotropic effects). LB46 itself produces tracheal relaxation which may result from an indirect sympathomimetic action. The influence of uptake into adrenergic nerves on pA2 and pA10 values for LB46 and propranolol, when using norepinephrine as an agonist drug, has been assessed from results obtained on trachea in the presence and absence of cocaine. In the absence of cocaine, the slopes of the regression of log (dose ratio -1) against negative log molar concentration of antagonist were less than the theoretical value of -1.0. In the presence of cocaine the slopes of these regressions approached -1.0. Thus values of (pA2 - pA10) also deviated from the theoretical value in the absence of cocaine but approached it if cocaine was present in the bath fluid. 19 references. (author abstract)

40752
AUTHORS: de Groat, William C.
TITLE: The actions of gamma-aminobutyric acid and related amino on mammalian autonomic ganglia.
SOURCE: Journal of Pharmacology and Experimental Therapeutics.
SOURCEID: 172(2):384-396, 1970.

An electrophysiologic study was made of the effects of gamma-aminobutyric acid (GABA) and related amino acids on automonic ganglia of the cat and rabbit. In the superior cervical ganglion of the cat, i.a. administration of GABA evoked a negative ganglionic surface potential and depressed nicotinic and muscarinic ganglionic transmission as well as the ganglionic responses to injected

muscarinic stimulating agents. GABA exhibited similar depressant actions in other autonomic ganglia. These effects were antagonized by picrotoxin but were unaffected by strychnine, cholinergic blocking agents or chronic preganglionic denervation. Other amino acids including gamma-amino-beta-hydroxybutyric acid, 3-amino-1-propanesulfonic acid and beta-alanine mimicked many of the ganglionic effects of GABA; however, glycine, a potent depressant of spinal neurons, was inactive. The results indicate that amino acids react with receptor sites on ganglion cells to elicit a reduction in resting membrane potential and a depression of membrane excitability. The antagonism between picrotoxin and GABA in ganglia represents the 1st demonstration of this interaction in the mammalian nervous system and raises the possibility that a similar pharmacologic antagonism may yet be discovered at sites in the mammalian central nervous system. 49 references. (author abstract)

40753
AUTHORS: Peach, M. J.; Ford, G. D.; Azzaro, A. J.; Fleming, W. W.
TITLE: The effects of acidosis on chronotropic responses, norepinephrine storage and release in isolated guinea-pig atria.
SOURCE: Journal of Pharmacology and Experimental Therapeutics.
SOURCEID: 172(2):289-296, 1970.

Effects of acidosis on chronotropic responses, norepinephrine storage and release were studied in isolated guinea pig atria. Spontaneously beating right atria were placed in baths at 30 C, pH of approximately 7.65 or 7.00, and cumulative dose response curves were obtained with tyramine or norepinephrine. Decreased pH had no effect on the spontaneous atrial rate or on responses to norepinephrine. Chronotropic responses to tyramine, however, were markedly decreased at the lower pH. Since responses to norepinephrine were affected by increased hydrogen ion, there was no acidosis induced alteration in chronotropic adrenergic receptors. There was a significant decrease in atrial norpinephrine when the pH was reduced. H3-norepinephrine uptake and turnover studies were carried out. A pH induced increased in atrial H3-norepinephrine turnover occurred and was not blocked by cocaine. At the lower pH, H3-norepinephrine retention was reduced and H3 deaminated metabolites increased, indicating uptake inhibition at the level of storage granule. The changes in norepinephrine storage and decreased tyramine induced release of H3-norepinephrine at pH 7.00 suggest decreased availability of releasable norepinephrine, which would explain the depressed chronotropic responses to tyramine in acidosis. 26 references. (author abstract modified)

40754
AUTHORS: Watrous, William M.; May, David G.; Fujimoto, James M.
TITLE: Mechanism of the renal tubular transport of morphine and morphine ethereal sulfate in the chicken.
SOURCE: Journal of Pharmacology and Experimental Therapeutics.
SOURCEID: 172(2):224-229, 1970.

The Sperber chicken preparation was used to study the transport systems involved in the renal tubular transport of morphine and its metabolite, morphine ethereal sulfate. Cyanine 863 and mepiperphenidol were potent inhibitors of morphine transport. N-Methylnicotinamide exerted little inhibitory effect, presumably because it has lower affinity for the transport mechanism. Probenecid had no effect on morphine transport or on the excretion of morphine ethereal sulfate formed in the kidney but effectively blocked transport of infused radioactive morphine ethereal sulfate which had been prepared biologically and isolated in crystalline form. Since probenecid inhibited the transport of the infused metabolite but not the excretion of metabolite formed in renal cells, the functional site of action of probenecid is thought to be located only at the peritubular border of the cell. 18 references. (author abstract modified)

40755
AUTHORS: Maren, Thomas H.; Broder, Lawrence E.
TITLE: The role of carbonic anhydrase in anion secretion into cerebrospinal fluid.
SOURCE: Journal of Pharmacology and Experimental Therapeutics.
SOURCEID: 172(2):197-202, 1970.

The entry of total C(14)O(2) and Cl(36) from blood into cerebrospinal fluid (CSF) was studied in cats with ventriculocisternal perfusion both before and after the administration of acetazolamide, a carbonic anhydrase inhibitor. It was found that the normal animal accumulates total C(14)O(2) by hydration of carbon dioxide to HCO(3)-at 5 times the rate of the inhibited animal, a difference that cannot be explained by changes in CSF production alone. The rate of entry of Cl(36) in the normal animal was about twice that found in the inhibited animal, a change that was the same as that in CSF formation rate. It thus appears that both HCO(3)- formation and Cl- transport into the CSF depend on catalytic hydration of carbon dioxide, a process which may be important in the physiologic regulation of CSF acid - base equilibria and fluid production. 26 references. (author abstract)

40756
AUTHORS: Giacobini, E.; Karjalainen, K.; Kerpel-Fronius, S.; Ritzen, M.
TITLE: Monoamines and monoamine oxidase in denervated sympathetic ganglia of the cat.
SOURCE: Neuropharmacology (Oxford).
SOURCEID: 9(1):59-66, 1970.

Monoamine oxidase (MAO) activity and levels of norepinephrine fluorescence were studied in preganglionically denervated L7 ganglia and individual ganglion cells in anesthesized cats. The majority of the cells showed low MAO activity, while a few cell bodies had high activity. Preganglionic denervation did not change the frequency distribution pattern. Fluorescence was about 30% higher in the denervated cells than in the control, indicating a significant increase in catecholamine content following denervation. The deprivation of physiological stimuli and synaptic connections in the sympathetic neurons from L7 cat ganglion resulted in accumulation of the transmitter, norepinephrine, and an increase of the activity of the corresponding inactivation enzyme (MAO) in the cell body. 27 references. (author abstract modified)

41538
AUTHORS: Edge, N. D.
TITLE: The effect of antiadrenaline compounds on acetylcholine responses of frog rectus abdominis muscle.
SOURCE: British Journal of Pharmacology (London).
SOURCEID: 38(2):386-393, 1970.

Effects of 9 antiepinephrine compounds and ergometrine on acetylcholine (ACh) induced contractures of the frog isolated rectus abdominis muscle were investigated. Tolazoline caused potentiation in low concentrations. Higher concentrations of tolazoline antagonized contractures. None of the other compounds tested potentiated ACh responses. The results are discussed in the context of previous findings. 17 references. (author abstract modified)

41539
AUTHORS: Aviado, Domingo M.; Sadavongvivad, Chiravat.
TITLE: Pharmacological significance of biogenic amines in the lungs: noradrenaline and dopamine.
SOURCE: British Journal of Pharmacology (London).
SOURCEID: 38(2):374-385, 1970.

A study was made of the pharmacological significance of norepinephrine and dopamine in the lungs of the rabbit, cat, dog, and

goat. The norepinephrine concentration in the lung of these species produced a fall in pulmonary resistance which was reduced by the administration of reserpine or cocaine. Although an infusion in the cat lung of norepinephrine increased the content of this amine, previously depleted by reserpine, the bronchodilator property of tyramine was not restored. The infusion of isoprenaline did not restore the response to tyramine. The role of either catecholamine in mediating the bronchomotor response to tyramine could not be ascertained. The concentration of dopamine varied from 6.4mcg/gm in the goat to less than 0.5mcg/gm in the lungs of the cat, rabbit, dog, rat, mouse, guinea pig and man. Dopamine, injected intravenously into the cat, dog, rabbit, and goat, produced a slight rise in pulmonary resistance which was blocked by tolazoline, indicating that the response was mediated by alpha-adreno-receptors in the bronchial passages. 20 references. (author abstract modified)

41540
AUTHORS: Khan, I.; Qureshi, Z.; Haq, M.
TITLE: Study of the effects of progesterone therapy on the stilboestrol-induced sensitivity of isolated uteri of hypophysectomized rats.
SOURCE: British Journal of Pharmacology (London).
SOURCEID: 38(2):316-320, 1970.

Study of the effects of progesterone therapy on the stilbestrol induced sensitivity of isolated uteri of hypophysectomized rats shows that these effects are not dependent on the pituitary but on the ovary. It is suggested that the hypophysis does not play any part in the desensitization of the myometrium to the oxytocic drugs and in the changes found in the vaginal mucosa after progesterone therapy. 9 references. (author abstract modified)

41552
AUTHORS: Bhagat, B.
TITLE: Effects of chronic administration of nicotine on storage and synthesis of noradrenaline in rat brain.
SOURCE: British Journal of Pharmacology (London).
SOURCEID: 38(1):86-92, 1970.

A study was undertaken to determine the effect of chronic administration of nicotine on catecholamine concentrations in rat brain. Chronic administration of nicotine (0.5mg/kg, subcutaneously 4 times a day, 5 days a week, for 6 weeks) did not affect the growth rate and water intake in rats. Food intake was normal for the 1st 5 weeks but was significantly increased during the 6th week of treatment. The blood pressure was increased from 120 mm Hg to 151 mm Hg. The concentrations of endogenous norepinephrine, dopamine, 5-hydroxytryptamine and acetylcholine in the brain remained unaltered. However, chronic treatment with nicotine increased the turnover rate of norepinephrine. Initial accumulation of H(3)-norepinephrine was also significantly increased. It is concluded that changes in the turnover of cerebral norepinephrine caused by chronic administration rather than changes in the concentrations of norepinephrine may be an important factor in nicotine induced behavioral changes. 17 references. (author abstract modified)

41564
AUTHORS: Ash, A. S. F.; Toh, H. T.
TITLE: Oxidative phosphorylation in heart mitochondria isolated from chlorpromazine-treated animals.
SOURCE: British Journal of Pharmacology (London).
SOURCEID: 38(2):436P-438P, 1970.

Experiments on respiration of the mitochondria from guinea pigs, rats, and cats indicated that chlorpromazine -induced changes observed with freshly isolated mitochondria suggest an effect of the drug on the first phosphorylation complex of the electron transport

chain. Results with stored mitochondria indicate stabilization of the mitochondrial membrane. 4 references.

41565
AUTHORS: Sadavongvivad, Chiravat.
TITLE: Pharmacological significance of biogenic amines in the lungs: 5-hydroxytryptamine.
SOURCE: British Journal of Pharmacology (London).
SOURCEID: 38(2):353-365, 1970.

A technique has been developed for the spectrofluorometric analysis of the biogenic amines, 5-hydroxytryptamine, histamine, norepinephrine and dopamine, in a single lung sample. The procedure consists principally of disintegrating the lung tissue in butanol and subsequent separation of amines for measurement of fluorescence, either directly, as for 5-HT, or after formation of fluorophores, as for histamine, norepinephrine and dopamine. It has been possible to analyze all 4 amines from a sample of the lung in which the bronchopulmonary responses have been investigated. The concentration of 5-HT in the lung of 7 species ranges from about 0.5mcg/gm in the guinea pig, dog and man to about 7mcg/gm in the rabbit. The pulmonary resistance is increased after an injection of 5-HT in the rat and guinea pig. The guinea pig is more sensitive to 5-HT than is the rat. In both species, the content of 5-HT in the lung is elevated by administration of either 5-HT or 5-hydroxytryptophan. In the rat, the administration of p-chlorophenylalanine reduces the content of 5-HT in the brain but not in the lung. It is suggested that the 5-HT contained in the lung tissue is stored mainly in the platelets and in the mast cells. 31 references. (author abstract modified)

41566
AUTHORS: O'Keeffe, Ruth; Sharman, D. F.; Vogt, Marthe.
TITLE: Effect of drugs used in psychoses on cerebral dopamine metabolism.
SOURCE: British Journal of Pharmacology (London).
SOURCEID: 38(2):287-304, 1970.

A study was made of the quantitative aspects of changes in dopamine metabolism following the use of drugs liable to produce parkinsonism, and of the relation these changes may bear to motor abnormalities produced either in animals or man. Reserpine or oxypertine cause a loss of cerebral catecholamines in the brain of animals, whereas phenothiazines and butyrophenones cause an increase in turnover of dopamine. Though all the drugs tested caused temporary motor disabilities in animals, these bore no resemblance to human parkinsonism, even when treatment was continued for 7 weeks or more. 29 references.

41567
AUTHORS: Hall, G. H.
TITLE: Effects of nicotine and tobacco smoke on the electrical activity of the cerebral cortex and olfactory bulb.
SOURCE: British Journal of Pharmacology (London).
SOURCEID: 38(2):271-286, 1970.

Studies on the effects of nicotine and tobacco smoke on the electrical activity of the cerebral cortex and olfactory bulb of the cat demonstrate that nicotine is the principal pharmacological constituent of tobacco smoke as far as effects on the central nervous system are concerned. However, the use of specific nicotine antagonists, such as mecamylamine, and filters for removing nicotine indicated the presence in smoke of other agents capable of exerting a pharmacological response. Cigarette smoke contains approximately 5% carbon monoxide. When introduced into the lungs of cats pretreated with 2mg/kg mecamylamine, 2ml samples of 5% carbon monoxide caused changes in the electrocorticogram similar to those caused by smoke. Effects of nicotine or smoke were not modified by pretreatment with

2-4mg/kg chlorpromazine. However, 0.3mg/kg atropine prevented the cortical activation but not the behavioral arousal. 29 references. (author abstract modified)

41569
AUTHORS: Feldberg, W.; Lang, W. J.
TITLE: Effects of monoamine oxidase inhibitors and amphetamine on hypothermia produced by halothane.
SOURCE: British Journal of Pharmacology (London).
SOURCEID: 38(1):181-191, 1970.

An investigation in cats of the action of monoamine oxidase (MAO) inhibitors, tranylcypromine, pheniprazine, and pargyline, in preventing the hypothermia associated with halothane anesthesia presented evidence that even with intraventricular injection the MAO inhibitors must first be absorbed into the blood stream before they can prevent the hypothermia produced by halothane. The hypothermia was prevented by intraperitoneal or intraventricular injection of amphetamine in a dose as small as 1mg; intraperitoneal injections were sometimes more effective. The action of the MAO inhibitors may not be solely on the anterior hypothalamus and they may not act only through MAO inhibition. 18 references. (author abstract modified)

41570
AUTHORS: Cox, B. M.; Osman, O. H.
TITLE: Inhibition of the development of tolerance to morphine in rats by drugs which inhibit ribonucleic acid or protein synthesis.
SOURCE: British Journal of Pharmacology (London).
SOURCEID: 38(1):157-170, 1970.

An investigation was made of the inhibition of the development of tolerance to the analgesic effects of morphine in rats by a number of drugs, which have as a common property the ability to inhibit ribonucleic acid (RNA) or protein synthesis. The effects of the drugs on the incorporation of C(14)-lysine into rat brain protein, and C(14)-orotic acid into rat brain RNA were also measured. Actinomycin D, 6-mercaptopurine and 5-fluorouracil reduced acquisition of tolerance to morphine at doses which also produced significant inhibition of incorporation of orotic acid into brain RNA. Cycloheximide and puromycin also reduced the development of tolerance to the analgesic effect of morphine and the incorporation of lysine into brain protein. The results support the hypothesis that the synthesis of new RNA and protein in the brain is an essential feature of the development of tolerance to morphine in rats. 30 references. (author abstract modified)

41913
AUTHORS: Large, W. A.; Milton, A. S.
TITLE: The effect of acute and chronic morphine administration on brain acetylcholine levels in rat.
SOURCE: British Journal of Pharmacology (London).
SOURCEID: 38(2):451P-452P, 1970.

Earlier research by Hano, Kaneto and Kakunaga (1963) had demonstrated that mice do not exhibit certain symptoms of physical dependence when compared with the rat. This study concerns the concentrations of acetylcholine in the brains of rats during various phases of the tolerance cycle. Rats were made tolerant to morphine sulfate by i.p. injections and maintained at this level of treatment (100mg/kg) for a period of 6 to 10 weeks. A dose of nalorphine hydrobromide was substituted for a schedule dose of morphine. Control animals were injected with an 0.9% saline solution over the same period of time. The brains of all animals were excised and extracted for acetylcholine. The results show that whereas morphine causes an increase in brain acetylcholine when administered acutely, it no longer causes an increase in brain acetylcholine in morphinized rats. In morphinized rats, however, a rise in brain acetylcholine

can be induced by abrupt withdrawal of morphine or by precipitating the abstinence syndrome with nalorphine. 2 references.

41967
AUTHORS: Pacha, W.; Slazmann, H.
TITLE: Inhibition of the re-uptake of neuronally liberated noradrenaline and alpha-receptor blocking action of some ergot alkaloids.
SOURCE: British Journal of Pharmacology (London).
SOURCEID: 38(2):439P-440P, 1970.

Ergot alkaloids possess a wide spectrum of pharmacological activities with great differences in potency. Some, for example, have high alpha-receptor blocking activity, whereas others have little or no activity. This study concerns the effect of 1-methyl-ergotamine, ergotamine, Hydergine, dihydroergotamine and phenoxybenzamine on the norepinephrine content of the perfusate to their alpha-blocking activity. The results show a marked increase of the content of neuronally liberated norepinephrine can also be produced by ergot alkaloids which have only little alpha blocking activity. It is suggested that the increase of neuronally liberated norepinephrine which is observed with some ergot alkaloids is not due to a blockade of alpha-receptors, but to an inhibition of the reuptake. This effect of ergot alkaloids, little known to date, might be significant for the pharmacological characterization of these substances. 4 references.

41974
AUTHORS: Cowie, A. Louise; Kosterlitz, H. W.; Lydon, E. J.; Waterfield, Angela A.
TITLE: The effects of morphine-like substances and their antagonists on transmission at the neuro-effector junction of the myenteric plexus-longitudinal muscle preparation of the guinea-pig ileum.
SOURCE: British Journal of Pharmacology (London).
SOURCEID: 38(2):465P-466P, 1970.

Use was made of the guinea pig ileum to predict agonist and antagonist activities of new compounds. Since the method depends on the effects of the narcotic analgesic drugs on impulse transmission at the myenteric plexus longitudinal muscle junction, it was of interest to investigate more fully the factors which influence the release of acetylcholine and the response of the longitudinal muscle to the transmitter. It has been shown in earlier research that morphine in low concentrations depresses the acetylcholine output when the myenteric plexus longitudinal muscle preparation is stimulated at low frequencies (0.1 to 1 cps.) In the presence of morphine, the evoked output per volley is low and almost constant at frequencies between 0.1 and 10 cps., whereas without morphine the output per volley is usually higher at low frequencies of stimulation and falls with increasing rates of excitation. Electrophysical experiments appear to be in favor of such an interpretation. 5 references.

42726
AUTHORS: Bartholini, G.; Kuruma, I.; Pletscher, A.
TITLE: L-Dopa-induced accumulation of 3-O-methyldopa in brain and heart.
SOURCE: European Journal of Pharmacology (Amsterdam).
SOURCEID: 10(2):189-192, 1970.

Since dopa is administered to patients with parkinsonism for a long period of time, information on the pharmacodynamics of accumulating metabolites is of importance. Wistar rats were injected i.p. with various doses of labeled L-dopa and the radioactive metabolites in brain and heart were measured quantitatively and qualitatively. The results confirm earlier findings that in the brain, 1 to 2 hours or more after a single administration of

C14-dopa, the levels of C14-3-O-methyldopa are considerably higher than those of C14-dopa, catecholamines and phenolcarboxylic acids; 3-O-methyldopa increases and decreases rather slowly, remaining measurable for about 48 hours. In the heart, the concentration of C14-3-O-methyldopa attains about the same maximal value and has a similar time course as that in the brain. The slow decline of 3-O-methyldopa in the heart and brain indicates a slow clearance of this metabolite from these tissues, explaining its considerable accumulation after repeated administrations of L-dopa. 4 references.

42727
AUTHORS: Nyback, Henrik; Sedvall, Goran.
TITLE: Further studies on the accumulation and disappearance of catecholamines formed from tyrosine-14C in mouse brain. Effect of some phenothiazine analogues.
SOURCE: European Journal of Pharmacology (Amsterdam).
SOURCEID: 10(2):193-205, 1970.

The metabolic fate of catecholamines formed from C14-tyrosine administration to conscious mice was investigated, as well as the effects of promethazine, levomepromazine, chlorpromazine, perphenazine and chlorprothixene. The neuroleptic phenothiazine analogues, excluding the nonneuroleptic, promethazine accelerated the disappearance rates of both C14-dopamine and C14-nonadrenaline in mouse brain. The clinically most potent neuroleptic seemed to accelerate C14-dopamine disappearance somewhat more than C14-noradrenaline disappearance. During infusion of C14-tyrosine, all neuroleptics accelerated the accumulation of C14-dopamine more than that of C14-noradrenaline. It is suggested that neuroleptic phenothiazine analogues accelerate turnover of both dopamine and noradrenaline. Sedative properties might be better correlated to an increased synthesis and turnover of noradrenaline. 45 references. (author abstract modified)

42742
AUTHORS: Cheramy, A.; Besson, M. J.; Glowinski, J.
TITLE: Increased release of dopamine from striatal dopaminergic terminals in the rat after treatment with a neuroleptic: thioproperazine.
SOURCE: European Journal of Pharmacology (Amsterdam).
SOURCEID: 10(2):206-214, 1970.

The effects of thioproperazine pretreatment on dopamine synthesis and release were examined by measuring the simultaneous accumulation of tritiated dopamine in tissues and incubating medium after incubation of isolated cut striatum with tritiated tyrosine. Thioproperazine treatment in intact animals produced an almost immediate sustained increase in the synthesis of dopamine; this effect was associated with a markedly enhanced release of newly synthesized amine. Various data suggest that the drug indirectly activates nigrostriatal dopamine containing neurons through dopamine receptor blockade. Thioproperazine added directly onto isolated striatum did not affect release or synthesis of dopamine. Thioproperazine potentiated amphetamine induced release of dopamine, but it blocked the other pharmacological effects of amphetamine occurring in animals. 32 references. (author abstract modified)

42755
AUTHORS: Schubert, Johan; Nyback, Hendrik; Sedvall, Goran.
TITLE: Accumulation and disappearance of 3H-5-hydroxytryptamine formed from 3H-tryptophan in mouse brain: effect of LSD-25.
SOURCE: European Journal of Pharmacology (Amsterdam).
SOURCEID: 10(2):215-224, 1970.

Tritiated tryptophan was administered i.v. to conscious mice by injection or constant rate infusion. Endogenous tryptophan and 5-hydroxytryptamine (5-HT) levels were not significantly altered by

this treatment. Tritiated 5-HT formed in vivo from the labeled precursor was identified by paper chromatography. Following a pulse injection of tritiated tryptophan, the level of tritiated 5-HT in brain rapidly increased, reaching a peak within 30 min. Pretreatment of the animals with the tryptophan hydroxylase inhibitor, p-chlorophenylalanine or reserpine, markedly reduced the accumulation of tritiated 5-HT. Following the initial peak, the content of tritiated 5-HT declined over several hours at a rate that seemed to be exponential between 30 and 180 min after precursor administration with a half-life of about 60 min. Treatment with p-chlorophenylalanine 60 min after precursor administration did not accelerate the rate of disappearance of tritiated 5-HT, indicating that the decline of tritiated 5-HT content is predominantly determined by turnover of the amine. The procedures were used to study the effect of LSD-25 on mouse brain serotonin metabolism. Following LSD-25 treatment, the rates of accumulation and disappearance of tritiated 5-HT after tritiated tryptophan administration were markedly reduced. The contents of labeled tryptophan and endogenous tryptophan and 5-HT levelicate that LSD-25 reduces both synthesis and turnover of 5-HT in brain. The LSD-25 analogue BOL-148 (D-brom-lysergic acid diethylamide bitartrate) showed no effect on brain 5-HT metabolism. Possible mechanisms of action of LSD-25 are discussed. 25 references. (author abstract modified)

42840
AUTHORS: Yuwiler, A.; Geller, E.
TITLE: Influence of mode and duration of phenylalanine administration on biochemical parameters in rats of various ages.
SOURCE: Developmental Psychobiology.
SOURCEID: 2(4):240-246, 1970.

Blood and tissue levels of phenylalanine and tyrosine progressively increase during the first 2 weeks of feeding a phenylalanine-rich diet to weanling made Sprague-Dawley and Long-Evans rats. Concomitantly, liver phenylalanine hydroxylase activity and brain serotonin progressively decline and hepatic tryptophan hydroxylase activity drops quickly to a constant, low level. With the exception of tryptophan hydroxylase, all of these parameters return towards normal upon continuous treatment. The magnitude of change varies with the age of the animal at initiation of dietary treatment, and arises because of differences in effective dosage and metabolism as the animals mature. A single phenylalanine injection produces a transient elevation in tissue phenylalanine levels without appreciably affecting brain serotonin. Repeated phenylalanine injections produce more marked alterations in tissue phenylalanine and tyrosine levels, lower activity of tryptophan hydroxylase, and increase serum adrenocorticoids; phenylalanine hydroxylase activity and brain serotonin levels are only marginally affected. These changes seriously complicate interpretations of behavioral studies in experimental phenylketonuria. 24 references. (author abstract modified)

43276
AUTHORS: Paul, M. I.; Pauk, G. L.; Ditzion, B. R.
TITLE: The effect of centrally acting drugs on the concentration of brain adenosine 3prime,5prime-monophosphate.
SOURCE: Pharmacology (Basel).
SOURCEID: 3(3):148-154, 1970.

Adenosine 3prime,5prime-monophosphate (cyclic AMP) was measured in the brains of adult male NIH general purpose mice which had been treated with a variety of centrally active drugs and killed by decapitation or freezing in liquid nitrogen. Theophylline produced 2 effects; an increase in the cyclic AMP level in animals which were frozen, and a decrease in the cyclic AMP level in decapitated animals. Pentobarbital decreased the cyclic AMP levels of animals which were decapitated, but no such effect was seen in animals killed

by freezing. D-Amphetamine or pentylenetetrazole did not change the cyclic AMP concentration in mice killed either by decapitation or freezing. Treatment with beta-phenylisopropylhydrazine (a monoamine oxidase inhibitor) and L-dihydroxy-phenylalanine decreased the concentration of cyclic AMP in the brains of mice killed by decapitation but no effect was seen on animals killed by freezing. The relationship of brain cyclic AMP to carbohydrate metabolism is discussed. 13 references. (author abstract modified)

43277
AUTHORS: Greenspan, K.; Aronoff, M. S.; Bogdanski, D. F.
TITLE: Effects of lithium carbonate on turnover and metabolism of norepinephrine in the rat brain - correlation to gross behavioral effects.
SOURCE: Pharmacology (Basel).
SOURCEID: 3(3):129-136, 1970.

Monovalent lithium ion in a dose of 3mEq/kg more than doubled the rate of efflux of tritiated norepinephrine (NE3) from the brain of unanesthetized adult male Sprague-Dawley rats. The proportion of total radioactivity present as tritiated O-methylated-deaminated metabolite was increased at the expense of NE3. The increase in endogenous NE produced by pargyline was significantly lower than control. Monovalent lithium itself caused sedation, somnolence, ataxia and loss of weight, while in rats given pargyline (a monoamine oxidase inhibitor), lithium caused excitement, mydriasis, exophthalmos and tremors. The biochemical and pharmacological effects of lithium were observed at plasma levels of 0.35mEq/l. No changes in plasma sodium or brain sodium and potassium were observed. It is suggested that lithium interferes with the storage of brain norepinephrine causing increased turnover and metabolism. The pharmacological effects of lithium either correlate to a deficiency or to an excess of norepinephrine available to stimulate receptors, depending upon the presence of monamine oxidase inhibitor. 14 references. (author abstract modified)

45544
AUTHORS: Idanpaan-Heikkila, Juhana E.; McIsaac, William M.
TITLE: 2,5-Dimethoxy-4-methyl-amphetamine -- Tissue distribution and neurochemical action.
SOURCE: Biochemical Pharmacology.
SOURCEID: 19(3):935-937, 1970.

The tissue distribution and neurochemical action of2,5-dimethoxy-4-methylamphetamine (STP, DOM) were studied by labeling the compound with tritium in positions 3 and 6. Sixteen male mice and 6 pregnant mice received i.v. doses of H3-STP (14-28mg/kg) and sacrificed at 5 and 20 minutes, and at 1, 2, 6, and 24 hours. Autoradiography on the entire body section was performed; frozen organs were dissected and homogenized and their radioactivities were counted by liquid scintillation. STP effect on brain amine levels was determined in 44 female mice injected (10or50mg/kg, i.p.) with the drug (twelve control mice received saline), and whose brains were removed at 30, 60, and 120 minutes. Whole body tremor was the only major pharmacological effect recorded with STP. Five minutes after i.v. administration, the brain had twice the radioactivity of the blood, the highest concentration obtained at 20 minutes. This indicates that STP penetrates the blood-brain barrier rapidly and has an affinity for brain tissue. Large accumulations were found first in the cortex and later in both the white matter and thalamus. After 1 hour the hippocampus exhibited the highest radioactivity in the brain. Urine, kidney and liver showed (in decreasing order of content) the highest level of radioactivity. The high uptake of radioactivity in the salivary and lacrimal glands (up to 6 hours) suggests excretion of STP through these organs. STP crossed the placenta slowly and only traces were found. 11 references.

46137
AUTHORS: Zoglio, Michael A.; Maulding, Hawkins V.
TITLE: Complexes of ergot alkaloids and derivatives II: interaction of dihydroergotoxine with certain xanthines.
SOURCE: Journal of Pharmaceutical Sciences.
SOURCEID: 59(2):215-219, 1970.

Intermolecular complexation between a mixture of the comparatively water insoluble alkaloids comprising 9,10-dihydroergotoxine and several xanthines was investigated. Substantial elevations of aqueous solubility of dihydroergotoxine in 0.1 N hydrochloric acid and in pH 6.65 phosphate buffer were observed in most of the cases examined. This incongruity in the normally expected solubility data may be attributed to a mutual influence between the ergot derivative and the xanthine under consideration. Dissolution studies indicated a generally enhanced 1st order rate of solution in the presence of xanthine which seems to evidence some driving force pulling the drug into solution. Partitioning rates (aqueous to chloroform) are usually increased when xanthine is added to the 9,10-dihydroergotoxine at pH 6.65 and the reverse is true in 0.1 N hydrochloride. Biological data in cats and humans are in good agreement with physicochemical work. 14 references. (author abstract)

46144
AUTHORS: Stolman, Sheldon; Aston, Roy.
TITLE: Relationship of barbital disposition to auto-induced hypersusceptibility in the rat.
SOURCE: Biochemical Pharmacology (Oxford).
SOURCEID: 19(2):595-601, 1970.

Barbital sodium, administered intraperitoneally in 2 daily doses of 200mg/kg, was found to induce in the female rat a hypersusceptibility to later challenge doses of the drug which was present after 18 days and absent after 38 days of abstinence. Spectrophotometric and radiometric assays of barbital tissue levels at various times from 10 minutes to 360 minutes after drug administration revealed no differences in blood, brain or urinary barbiturate levels among control, hypersusceptible or post hypersusceptible animals. The data support the suggestion that induced hypersusceptibility does not result from changes in the disposition of barbiturate in vivo. It appears likely that this phenomenon results from central nervous system alterations in the localization of, or sensitivity to, the drug. 14 references. (author abstract modified)

46188
AUTHORS: Fleisher, Joseph H.; Harris, Larrel W.; Berkovitz, Phillip T.
TITLE: Dephosphorylation in vivo of brain acetylcholinesterase inhibited by isopropyl methylphosphonofluoridate (sarin).
SOURCE: Biochemical Pharmacology (Oxford).
SOURCEID: 19(2):421-426, 1970.

Intravenous injection of P(32)-isopropyl methylphosphonofluoridate (sarin) into rats resulted in inhibition of brain acetylcholinesterase (AChE) activity and phosphonylation of the enzyme. Spontaneous recovery from inhibition occurred between 0.5 hour and 48 hours in the sarin intoxicated animals in correlation with comparable dephosphorylation of sarin derived phosphorus bound to the enzyme. Injection of 44mg/kg of monoisonitrosoacetone into the sarin intoxicated rats resulted in significant reactivation of inhibited brain AChE over and above that occurring spontaneously, accompanied by additional dephosphorylation of enzymatically bound phosphorus. Loss of phosphorus in vivo took place exclusively as P(32)-isopropyl methylphosphonic acid. No significant loss of sarin derived P(32) bound to AChE as P(32)-methylphosphonate was apparent under these conditions. 14 references. (author abstract modified)

46189
AUTHORS: Alivisatos, Spyridon G. A.; Ungar, Frieda; Seth, Prahlad K.; Levitt, LeRoy P.
TITLE: Effect of reserpine on the incorporation in vivo of radioactivity from labeled serotonin and other 5-hydroxy-indole derivatives in mouse brain.
SOURCE: Biochemical Pharmacology (Oxford).
SOURCEID: 19(2):401-410, 1970.

The effect of reserpine on the incorporation in vivo of radioactivity from labeled serotonin and other 5-hydroxyindole derivatives was studied in mouse brain. After endocranial - intraventricular administration of labeled serotonin or 5-hydroxyindole-3-acetaldehyde into mice, radioactivity is incorporated into acid insoluble material obtained from the brains of the animals. Under proper experimental conditions, pretreatment with pargyline diminishes the incorporation from serotonin, but incorporation from the aldehyde level remains unaffected. Radioactivity due to acid soluble metabolites obtained from the brain is higher after endocranial injection of serotonin into pargyline pretreated animals than in untreated controls. This effect is not observed after administration of the corresponding aldehyde. Pretreatment with reserpine greatly increases the radioactivity due to soluble metabolites in the acid washings and of the incorporation both at the serotonin and the aldehyde levels. This effect may be observed over a wide range of dosages. In reserpine pretreated animals, increased radioactivity in the washings is also observed after endocranial injection of a variety of other labeled compounds, including tryptamine, dl-norepinephrine, dopamine, l-lysine and 5-hydroxyindole-3-acetic acid. Thepossible mechanism of this effect is discussed. 31 references. (author abstract modified)

46191
AUTHORS: Vachon, Marc; Marchand, Claude.
TITLE: The influence of morphine on magnesium metabolism in rats.
SOURCE: Journal of Pharmacology and Experimental Therapeutics.
SOURCEID: 172(1):122-127, 1970.

The influence of morphine on magnesium metabolism was studied in rats. Intravenous administration of 2mg/kg morphine sulfate caused an increase in serum magnesium. A dose - response curve was obtained up to 16mg/kg. The hypermagnesemia reached a peak 1 hour after injection of the narcotic. It then slowly decreased, to return to normal values 6 hours after morphine administration. Nalorphine hydrochloride, which was slightly effective by itself, antagonized the hypermagnesemia when administered simultaneously with the agonist. After intravenous administration of Mg-28, specific activity of serum, bone and muscle in morphine treated rats increased. These results indicate that morphine has a marked effect on magnesium metabolism in rats. 18 references. (author abstract modified)

46196
AUTHORS: Ho, Beng T.; McIsaac, William Hallinson; An, Rong; Tansey, L. Wayne; Walker, K. E.
TITLE: Effect of amphetamine analogs on disruption of animal behavior and barbiturate sleeping time.
SOURCE: In: Harris, R., Drug dependence.
SOURCEID: Austin, University of Texas Press, 1970. 342 p. (p. 13-20).

The effect of amphetamine analogs on disruption of animal behavior and barbiturate sleeping time was studied in mice. Hallucinogens are grouped structurally into phenethylamineanalogs, phenylisopropylamine analogs, indole analogs, and neutral compounds. The structures of known hallucinogens are closely related to those of biogenic amines which are believed to be responsible for behavioral changes. The effect of 15 amphetamine analogs structurally related to STP (2,5-dimethoxy-4-methylamphetamine) was studied in mice. The swim maze test proved applicable as a qualitative measurement of the

disruption of animal behavior. The effects of these amphetamine analogs on barbiturate sleeping time in mice are presented in tabular form. The conversion of the 3,4-dimethoxy groups of the amphetamine molecule to a 3,4-methylenedioxy linkage results in stimulation, while replacement of 4-OCH3 by the OH group results in a compound that potentiates sleeping time. 5 references.

46197
AUTHORS: Tacker, Martha M.; Creaven, Patrick J.; McIsaac, William Mallinson.
TITLE: Preliminary observations on the metabolism of (3)H-2,5-dimethoxy-4-methyl-amphetamine (STP, DOM).
SOURCE: In: Harris, R., Drug dependence.
SOURCEID: Austin, University of Texas Press, 1970. 342 p. (p. 21-23).

The metabolism of (3)H-2,5-dimethoxy-4-methylamphetamine (STP, DOM) was studied in rats and rabbits. (3)H-STP (5mg/kg) was given to rats by intraperitoneal injection and the radioactive excretion followed for 96 hours. The same dose was given to rats in which a cannula had been placed in the bile duct at operation. The excretion of radioactivity was also measured in rabbits which had received 5mg/kg (3)H-STP intraperitoneally. In preliminary studies of urinary metabolites, 8 radioactive compounds present in rat urine were separated by 2 dimensional chromatography. The major urinary metabolite was an unconjugated compound of the major metabolite accounting for 38.81% of urinary radioactivity. In the rabbit, metabolites of STP in which the amine group had been lost or modified accounted for about 25% of the urinary radioactivity. It was established that sufficient unchanged STP is excreted in the urine for detection purposes.

46198
AUTHORS: Idanpaan-Heikkila, Juhana Elias; Fritchie, G. Edward; McIsaac, William Mallinson.
TITLE: Pharmacological and behavioral studies of STP: relationship to tissue distribution.
SOURCE: In: Harris, R., Drug dependence.
SOURCEID: Austin, University of Texas Press, 1970. 342 p. (p. 24-35).

The tissue distribution and elimination of (3)H-labeled STP (2,5-dimethoxy-4-methylamphetamine) was studied in mice and cats in an attempt to correlate its behavioral and pharmacological actions with the sites of accumulation in the brain. Male and pregnant female mice were given 28mg/kg (for males) or 14.0mg/kg (for females), intravenously. Six cats (1 female) were given 10mg/kg (3)H-STP, infused into the femoral vein. Frozen tissue sections were prepared and (3)H-STP was identified by thin layer chromatography. In mice, tremor of the whole body was the major pharmacological effect noted. Peak (3)H-STP concentration in the brain was obtained 20 minutes after administration, and this level was maintained up to 2 hours. This indicates that STP has a relatively high affinity for brain tissue. In cats, a catatonic state was produced, followed by tremor. The possibility that STP has an adrenergic beta receptor antagonizing effect is advanced. High concentrations of STP were found in certain brain areas and behavioral disturbances were noted that could be related to these same brain areas. Tables present the radioactivity distribution in mouse and cat tissue. 17 references.

46201
AUTHORS: Idanpaan-Heikkila, Juhana Elias; Schoolar, Joseph Clayton; Allen, Alton H.
TITLE: Total body kinetics and placental transfer of labeled LSD in mice.
SOURCE: In: Harris, R., Drug dependence.
SOURCEID: Austin, University of Texas Press, 1970. 342 p. (p. 55-66).

The question of the possibility of the passage of lysergic acid diethylamide (LSD) or its metabolites from maternal blood through the

placenta into the fetus was studied inmice. The kinetics of LSD in whole animal sections was studied to discover any particular accumulation sites, using the Ullberg total body autoradiographic method, liquid scintillation, and thin layer chromatography. A dose of 9.9mg/kg of (14)C labeled LSD was administered intravenously. Behavioral and pharmacological effects were recorded; studies of total body kinetics were begun 5 minutes after injection. Sites of high LSD accumulation include the brain, thalamus, hippocampus, adrenal glands, hypophysis, thyroid, thymus, ovaries, testes, bone marrow, lymph nodes, salivary glands, and lacrimal glands. Placental transfer of LSD was studied in the 1st and last weeks of pregnancy. LSD is capable of crossing mouse placenta, and its potential teratogenic effects can be the direct action of LSD itself on the fetus. The transfer of LSD is quantitatively dependent on the stage of pregnancy, being higher during the 1st week of pregnancy. 25 references.

46208
AUTHORS: Goldberg, Steven Robert.
TITLE: Relapse to opioid dependence: the role of conditioning.
SOURCE: In: Harris, R., Drug dependence.
SOURCEID: Austin, University of Texas Press, 1970. 342 p. (p. 170-197).

The physiological and behavioral disturbances precipitated when the chronic morphine treatment of a dependent organism is abruptly discontinued were studied in rhesus monkeys. The experiments demonstrated that environmental stimuli, when associated with nalorphine induced abstinence, can become conditioned stimuli capable of eliciting a variety of responses indicative of the abstinence syndrome. These conditional changes could be elicited,undiminished in strength, after 1 to 4 months of complete morphine abstinence. Finally, the conditioned stimuli associated with nalorphine induced abstinence are capable of producing large increases in the rate of morphine self-administration by rhesus monkeys. The results lend credence to theories relating conditioned abstinence phenomena to the problem of relapse. Criteria for the development of treatment programs are suggested. 67 references.

46399
AUTHORS: de Moura, Roberto Soares; de Souza Martins, S. A.; Sollero, L.
TITLE: Action of guanethidine on the pressor effect of angiotensin in adrenalectomized dogs.
SOURCE: Pharmacology (Basel).
SOURCEID: 3(1):15-20, 1970.

In order to check the adrenal participation of the potentiation of angiotensin by guanethidine, a study was undertaken to see how guanethidine modifies the pressor effect of angiotensin in adrenalectomized dogs. Adrenalectomy does not reduce the pressor effect of angiotensin. After adrenalectomy, guanethidine produces a significant augmentation of the pressor effect of angiotensin. Results suggest that the augmentation is independent of the adrenals and can be due to the indirect effect of angiotensin on the adrenergic nerve terminals. 16 references.

46400
AUTHORS: Helfer, H.; Jaques, R.
TITLE: Drug-dependent differences in the development of tolerance to writhing in mice.
SOURCE: Pharmacology (Basel).
SOURCEID: 3(1):41-52, 1970.

Male albino mice were injected daily with phenylquinone (PQ) in an experiment to study the development of tolerance to writhing. Whereas repeated injections of PQ rapidly lead to the development of tolerance to writhing, the writhing response to arachidonic acid

peroxide injected repeatedly does not decrease but actually increases. Mice rendered tolerant to PQ still respond to AAP (arachidonic acid peroxide) like untreated animals. 10 references.

46401
AUTHORS: Mule, S. J.
TITLE: Morphine and the incorporation of 32orthophosphate in vivo into phospholipids of the guinea pig cerebral cortex, liver and subcellular fractions.
SOURCE: Biochemical Pharmacology (Oxford).
SOURCEID: 19(2):581-593, 1970.

In experiments on the guinea pig cerebral cortex, it was concluded that morphine alters phospholipid metabolism in vivo and thus may directly affect cellular function in liver and neuronal activity in the central nervous system. Morphine had both an inhibitory and stimulatory effect on the total radioactivity determinations of mitochondrial subfractions from the cerebral cortex at 16, 24, and 48 hours. A statistically significant stimulatory effect was observed with individual phospholipids at 48 hours from the smooth and rough microsomal liver subcellular fractions. 38 references.

46402
AUTHORS: Coutinho, C. B.; Cheripko, J. A.; Carbone, J. J.
TITLE: Correlation between the duration of the anticonvulsant activity of diazepam and its physiological disposition in mice.
SOURCE: Biochemical Pharmacology (Oxford).
SOURCEID: 19(2):363-379, 1970.

Mice were studied for correlation between the duration of the anticonvulsant activity of diazepam and its physiological disposition. Maximal protection for 6 hours against a standard 125mg/kg subcutaneous convulsant dose of metrazole was afforded by a single 2.5mg/kg oral dose of diazepam. Differential analyses of blood, brain, and muscle tissue samples for diazepam and 3 of its major metabolites show that, although the concentration of each component at 30 minutes is similar both in the absence and presence of metrazole, a definite shift in the slope of the fall-off patterns toward a slower rate of disappearance of the parent compound and of its hydroxylated and desmethylated derivatives is evident when the administration of diazepam is followed by a subcutaneous injection of metrazole. 16 references.

46404
AUTHORS: Banerjee, U.; Burks, T. F.; Feldberg, W.; Goodrich, Cecilie A.
TITLE: Temperature responses and other effects of 5-hydroxytryptophan and 5-hydroxytryptamine when acting from the liquor space in unanaesthetized rabbits.
SOURCE: British Journal of Pharmacology (London).
SOURCEID: 38(4):688-701, 1970.

In unanesthetized rabbits 5-HTP (5-hydroxytryptophan) and 5-HT (5-hydroxytryptamine) were injected into the cisterna magna or into the cannulated left lateral cerebral ventricle while rectal temperature was recorded. 5-HTP injected intracisternally produced a fall, followed by a rise in temperature. Following an intracisternal injection of 1-4mg 5-HT, there was either a fall, or a fall followed by a rise; occasionally there was mainly a rise in temperature. Sites where 5-HTP and 5-HT act when producing the temperature responses and the various behavioral effects are discussed. 23 references. (author abstract modified)e

47325
AUTHORS: Haley, Thomas J.; Gidley, Joy T.

TITLE: Pharmacological comparison of R(+), S(-) and racemic secobarbital in mice.
SOURCE: European Journal of Pharmacology (Amsterdam).
SOURCEID: 9(3):358-361, 1970.

Pharmacological tests in male mice of the CF 1 strain demonstrated differences in potency between the stereoisomers of secobarbital. The S(-) antipode was a more potent anesthetic than either the R(+) antipode or the racemic mixture. The S(-) isomer was also the most toxic and the R(+) the least toxic. As anticonvulsants, both compounds were equipotent against pentylenetetrazol and strychnine induced seizures but the S(-) isomer protected the animals for a longer time interval than the R(+) isomer. The differences in potency between the enantiomorphs may be related to differences in ability to penetrate to the active site for narcosis and to remain there for a more extended period before metabolism and excretion takes place. This investigation establishes the fact that steric effect is important in the pharmacodynamics of barbituric acid derivatives. 10 references. (journal abstract modified)

47506
AUTHORS: Bowers, Malcolm B., Jr.
TITLE: CSF homovanillic acid: effects of probenecid and alpha-methyltyrosine.
SOURCE: Life Sciences.
SOURCEID: 9(12):691-694, 1970.

Probenecid increases the levels of the acid monoamine metabolite homovanillic acid (HVA) from dopamine in the cerebrospinal fluid (CSF). The effect of alpha-methyltyrosine (AMT), an inhibitor of catecholamine synthesis, upon these levels of CSF HVA was determined in anesthetized cats with a needle inserted into the cisterna magna. Following administration of probenecid 200mg/kg i.p., serial samples of 1 ml were obtained. In 2 hours, the level of CSF HVA after probenecid was 3 times the control value. Prior administration of 100mg/kg i.p. AMT reduced baseline levels of CSF HVA and prevented any significant rise of these levels following probenecid. Probenecid blockage of the efflux mechanism for HVA results in an increase of this monoamine metabolite in the CSF due to continuing dopamine synthesis and catabolism. Thus, probenecid blockade may be utilized in human experiments to separate the processes of influx and efflux upon CSF acid monoamine metabolite levels. This CSF HVA value may be ascribed to continuing endogenous production of HVA in the central nervous system. 6 references.

38488
AUTHORS: Ho, Beng T.; McIsaac, William M.; An, Rong; Tansey, L. Wayne; Walker, K. E.; Englert, Leo F., Jr.; Noel, Michael B.
TITLE: Analogs of alpha-methylphenethylamine (amphetamine). I. Synthesis and pharmacological activity of some methoxy and/or methyl analogs.
SOURCE: Journal of Medicinal Chemistry.
SOURCEID: 13(1):26-30, 1970.

A series of amphetamine derivatives substituted on the benzene ring with MeO and/or Me groups was synthesized. The pharmacological activity of these compounds was examined in terms of toxicity, effect on barbiturate sleeping time and ability to disrupt behavior of mice in a maze swimming test. Both reduction and potentiation of barbiturate sleeping time were observed. Several which reduced the sleeping time were rather toxic. Those active in disruption of behavior included 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane, 1-(2,4,5-trimethoxyphenyl)-2-aminopropane, 1-(2,4-dimethoxy-3-methylphenyl)-2-aminopropane, and 1-(3,4-methylenedioxyphenyl)-2-aminopropane. 15 references. (author abstract modified)

40578
AUTHORS: Igic, R.; Stern, P.; Basagic, Enisa.
TITLE: Changes in emotional behaviour after application of cholinesterase inhibitor in the septal and amygdala region.
SOURCE: Neuropharmacology (Oxford).
SOURCEID: 9(1):73-75, 1970.

Local application of the cholinesterase inhibitor, amiton, in the septum pellucidum caused an increased aggressiveness and hyperreactivity, and in some cases the mouse killing reaction, in the rat. The increased reactivity was depressed by atropine. Amiton application to the amygdala also leads to increased reactivity, with atropine having a depressant effect. Septal lesion performed previous to amiton application did not change the increased reactivity to any great extent, provided the cholinesterase inhibitor was applied locally to the basolateral part of the amygdala. 15 references. (author abstract modified)

40581
AUTHORS: Christmas, A. J.; Maxwell, D. R.
TITLE: A comparison of the effects of some benzodiazepines and other drugs on aggressive and exploratory behaviour in mice and rats.
SOURCE: Neuropharmacology (Oxford).
SOURCEID: 9(1):17-29, 1970.

Chlordiazepoxide, diazepam, nitrazepam and oxazepam were compared with amobarbital and meprobamate for their effects on aggressive behavior and their anticonvulsant activity in mice and rats, and for effects on ambulation of rats in the open field situation. All 4 benzodiazepines prevented aggressive behavior in the mouse and rat at doses well below those required to produce analgesia or sedation. Amobarbital and meprobamate showed little activity in reducing aggressive behavior. In rats with lesions in the midbrain, diazepam and nitrazepam reduced irritability at moderate doses. All compounds were potent anti-convulsants, but showed greater activity against pentylenetetrazole induced convulsions than against those incuded by maximal electroshock. They all significantly increased the ambulation of rats placed for the 1st time in the open field situation; however, amobarbital, meprobamate and oxazepam failed to increase ambulation significantly in rats repeatedly exposed to the open field and chlordiazepoxide produced a small but significant increase. 24 references. (author abstract modified)

40758
AUTHORS: Wuttke, W.; Kelleher, R. T.
TITLE: Effects of some benzodiazepines on punished and unpunished behavior in the pigeon.
SOURCE: Journal of Pharmacology and Experimental Therapeutics.
SOURCEID: 172(2):397-405, 1970.

The effects of some benzodiazepines on punished and unpunished behavior are studied in the pigeon. One group of pigeons responded under a 5 minute fixed interval schedule of food presentation, with every 30th response producing an electric shock (punishment group). Another group responded under the same schedule of food presentation, but without electric shock (nonpunishment group). All birds showed the usual fixed interval pattern of responding. Although the average rate of responding was much lower in the punishment group, the lowest rates (at the start of the interval) for the nonpunishment group were comparable to the highest rates (at the end of the interval) for the punishment group. Chlordiazepoxide, diazepam and nitrazepam markedly increased average rates of responding in the punishment group but only slightly increased those in the nonpunishment group. In birds of both groups, the proportional increases in rates of responding in 10ths of the fixed interval were inversely related to control rates of responding. Where rates of responding were comparable for the 2 groups, increases produced by the benzodiazepines were comparable. In contrast, imipramine increased rates of responding in the nonpunishment group, but decreased them in the punishment group. The results suggest that the benzodiazepines tend to increase relatively low rates of responding regardless of how these rates are established. 27 references. (author abstract modified)

41541
AUTHORS: Shillito, Elizabeth E.
TITLE: The effect of parachlorophenylalanine on social interaction of male rats.
SOURCE: British Journal of Pharmacology (London).
SOURCEID: 38(2):305-315, 1970.

Studies on the effects of parachlorophenylalanine on male rats showed that hair loss around the head and neck seems to be caused by increased social behavior in the form of chasing, rolling over and social grooming as a result of treatment with this drug. This change in behavior was counteracted by treatment with 5-hydroxytryptamine. The increase in social interaction seen in juvenile rats may be the precursor of adult sexual behavior. It is concluded that 5-hydroxytryptamine inhibits sexual behavior in male rats. 11 references. (author abstract modified)

42719
AUTHORS: Frankenheim, J. M.; McMillan, D. E.
TITLE: Behavioral effects of halothane in pigeons.
SOURCE: European Journal of Pharmacology (Amsterdam).
SOURCEID: 10(2):168-177, 1970.

It is possible to shape and control behavior by scheduling the consequences of behavior of an organism. This type of behavior is very stable and reproducible. By the appropriate scheduling of reinforcers, wide ranges in the rates and patterns of schedule controlled behavior can be studied. Eight male pigeons were trained to peck a key to obtain intermittent access to food, and the effects of various concentrations of halothane on the steady rate of key pecking generated by the schedule of food presentation were determined. Concentrations of halothane as low as 0.1%decreased the rate of key pecking, and higher concentrations decreased it further. Increases in the rate of pecking were not observed during halothane administration under several schedules of food presentation. The effects of halothane were also determined on the gross behavior of the pigeons using a blind technique. Although only the presence or

absence of changes in the gross behavior were recorded, these data were useful in interpreting the effects of halothane in key pecking. 16 references. (author abstract modified)

42837
AUTHORS: Wolf, Harold H.; Rowland, Clayton H.
TITLE: Effects of chronic postnatal drug administration on adult dominance behavior in two genera of mice.
SOURCE: Developmental Psychobiology.
SOURCEID: 2(4):195-201, 1970.

The influence of early chronic treatment with amphetamine or chlorpromazine on the formation of adult dominance behavior was studied in two genera of mice (i.e., Peromyscus maniculatus bairdi and a randomly bred Swiss albino strain of Mus musculus). Amphetamine - pretreated Swiss albinos were significantly more dominant than either chlorpromazine - pretreated or control animals. Early drug treatment had little effect on dominance behavior of adult bairdi. Chronic administration of certain drugs of young animals appears to produce a quantitative change in the formation of adult behavior patterns; the degree to which early drug treatment alters adult behavior may be influenced by the genetic background of the organism is supported by the data of this study. 31 references. (author abstract modified)

45526
AUTHORS: Caldwell, D. F.; Oberleas, D.; Clancy, J. J.; Prasad, A. S.
TITLE: Behavioral impairment in adult rats following acute zinc deficiency.
SOURCE: Proceedings of the Society for Experimental Biology and Medicine.
SOURCEID: 133(4):1417-1421, 1970.

Behavioral measures were obtained for 24 rats administered a zinc deficient diet (8.0mg/kg) and adequate in all other constituents for 48 days beginning at age 30 days. Pair -fed controls received a zinc supplemented diet (70mg/kg of total zinc). Lethargy and reduced weight gain were characteristic of all zinc deficient subjects. Performance on 2 measures of learning ability (a one way conditioned avoidance test and an 8 blind water maze) and test of activity - emotionality (the open field test) revealed zinc deficient animals to be inferior when compared to zinc supplemented subjects. The relationship between zinc and protein use is a possible mechanism explaining the effects of zinc insufficiency. 16 references. (author abstract modified)

46139
AUTHORS: Funderburk, W. H.; Foxwell, Marianne H.; Hakala, M. W.
TITLE: Effects of psychotherapeutic drugs on hypothalamic-induced hissing in cats.
SOURCE: Neuropharmacology (Oxford).
SOURCEID: 9(1):1-7, 1970.

The effects of psychotherapeutic drugs on hypothalamic induced hissing elicited by stimulating the perifornical region of the hypothalamus in 4 cats with chronically implanted electrodes was studied. Pentobarbital (10mg/kg), ethomoxane (2.5mg/kg) and chlordiazepoxide (10mg/kg) raised the hissing threshold. The antidepressant drugs, imipramine, desipramine and amitriptyline given in doses of 5mg/kg raised this threshold, whereas 2.5mg/kg chlorpromazine or Triperidol (trifluperidol) lowered the threshold. A larger dose (5mg/kg) of Chlorpromazine produced the same effect. Daily doses of 2.5mg/kg chlorpromazine for 3 days decreased the hissing threshold more markedly. Different results were obtained with piperazinophenothiazines; the results were inconsistent following 1mg/kg perphenazine, and 1mg/kg and 2mg/kg trifluoperazine raised the threshold for hissing. 19 references. (author abstract modified)

46142
AUTHORS: Vasquez, Beatriz J.; Izquierdo, Ivan.
TITLE: The effect of amphetamine, nicotine and atropine on pseudoconditioned responses of rats.
SOURCE: Pharmacology (Basel).
SOURCEID: 3(1):21-24, 1970.

The effect of amphetamine, nicotine and atropine on pseudoconditioned responses (probability of response to a neutral stimulus increased by the unpaired presentation of another stimulus, electric shock, which normally elicits the observed response) was studied in the rat. Amphetamine was found to increase the incidence of pseudoconditioned responses of the rats to a buzzer. Atropine, which had no effect of its own, potentiated that of amphetamine. Nicotine, either given alone or in combination with atropine, was ineffective. These results cannot be correlated with the effect of these drugs on hippocampal evoked electrical activity, nor with the effect of conditioning, amphetamine and nicotine as opposed to pseudoconditioning, on hippocampal ribonucleic acid concentration. Therefore, it is considered likely that the hippocampus is not involved either in pseudoconditioning or in the effects of drugs on pseudoconditioning. 10 references. (author abstract modified)

46143
AUTHORS: Yen, H. C. Y.; Krop, S.; Mendez, Halina C.; Katz, M. H.
TITLE: Effects of some psychoactive drugs on experimental 'neurotic' (conflict induced) behavior in cats.
SOURCE: Pharmacology (Basel).
SOURCEID: 3(1):32-40, 1970.

The effects of psychoactive drugs on conflict induced neurotic behavior were studied in cats. The animals were trained to obtain a reward of food pellets in a conditioning apparatus and established a normal and regular cycle of response in 2 to 6 weeks. The cats were rendered neurotic by subjection to randomly occurring air blasts at the reward box. Behavior of the conditioned cats was noted after oral administration of the following drugs: 50mg/kg meprobamate 5 times on alternate days, 10-15mg/kg pentobarbital sodium, 10-20mg/kg phenobarbital, 3-6mg/kg chlorpromazine, 6-10mg/kg chlordiazepoxide, 3-6mg/kg diazepam, or 0.5-1.0mg/kg haloperidol. All drugs reduced or abolished the phobic reaction at these dosages. d-Amphetamine facilitated development of the neurotic behavior within 0.5 to 1 hour, but had little or no effect in cats pretreated with hypnotics and tranquilizers. 24 references. (author abstract modified)

46186
AUTHORS: Evangelista, A. M.; Gattoni, R. C.; Izquierdo, Ivan.
TITLE: Effect of amphetamine, nicotine and hexamethonium on performance of a conditioned response during acquisition and retention trials.
SOURCE: Pharmacology (Basel).
SOURCEID: 3(2):91-96, 1970.

Rats were trained for acquisition of a conditioned avoidance response and tested for retention of this response 5 days later to determine the effects of amphetamine, nicotine, and hexamethonium on performance. When injected prior to acquisition, nicotine and hexamethonium produced improved retention, and amphetamine and nicotine enhanced performance of the learned response during acquisition. When injected immediately after acquisition, the 3 drugs resulted in increased retention. 18 references. (author abstract modified)

46190
AUTHORS: Pradhan, S. N.; Dutta, S. N.
TITLE: Comparative effects of nicotine and amphetamine on timing

behavior in rats.
SOURCE: Neuropharmacology (Oxford).
SOURCEID: 9(1):9-16, 1970.

The effects of 0.05mg/kg, 0.1mg/kg, 0.2mg/kg and 0.3mg/kg of nicotine and 0.2mg/kg, 0.4mg/kg, and 0.8mg/kg amphetamine were tested on the timing behavior in rats. Both the drugs caused an increase in the number of bar pressing responses and a decrease in reinforcement, and thus disruptes the timing behavior. No consistent delayed effect was observed with these doses. With both drugs, a rough dose - effect relation could be demonstrated, and the interresponse time distributions were found to be shifted to the shorter class intervals, consistent increase occurring in the intermediate interval group. 7 references. (author abstract modified)

46206
AUTHORS: Thompson, Travis Irving; Pickens, Roy Wilson.
TITLE: Behavioral variables influencing drug self-administration.
SOURCE: In: Harris, R., Drug dependence.
SOURCEID: Austin, University of Texas Press, 1970. 342 p. (p. 143-157).

Behavioral variables influencing drug self-administration are discussed. An understanding of the behavioral impact of drugs is predicated on knowledge of the major variables controlling behavior. These include antecedent conditions, current environmental circumstances, and response consequences. Ways in which these 3 classes of variables influence drug self-administration are examined, based on experiments with laboratory animals, notably rats and monkeys. Many of the variables controlling behavior in general were found to control drug self-administration. Knowledge of conditioning principles is useful in suggesting areas for future study. The characteristics of drugs as reinforcers may differ somewhat from other reinforcers to the same extent that other reinforcers differ among themselves. 33 references.

46207
AUTHORS: Woods, James Henry; Schuster, Charles Robert, Jr.
TITLE: Regulation of drug self-administration.
SOURCE: In: Harris, R., Drug dependence.
SOURCEID: Austin, University of Texas Press. 1970. 342 p. (p. 158-169).

Patterns of self-administration of central stimulants, narcotics, barbiturates, and ethanol were studied using rhesus monkeys under laboratory controlled conditions. It was shown that the pharmacological classes of the agents, unit dose, and access time each have distinct contributing characteristics that modify drug self-administration. Behavior regulates drug consumption and, in turn, the drug's effect regulates behavior. Continued analysis of this basic interaction in which reinforcement plays an essential role is recommended. 22 references. (author abstract modified)

46209
AUTHORS: Whitney, Glayde D.; Trost, James Gregory.
TITLE: Response disruption following amphetamine self- and programmed administration.
SOURCE: In: Harris, R., Drug dependence.
SOURCEID: Austin, University of Texas Press, 1970. 342 p. (p. 198-213).

Some variables relevant to the self-administration of d-amphetamine were studied. Dextroamphetamine sulfate was self-administered via a Talley device to relatively unrestrained macaque monkeys. The equipment and methods are described, and a report is given of the investigation of some variables relevant to the self-administration of the drug. The data suggest, but do not adequately establish, that amphetamine has negative reinforcing

properties or that it is aversive. 30 references.n

46210
AUTHORS: Harris, Robert T.; Balster, Robert L.
TITLE: An analysis of psychological dependence.
SOURCE: In: Harris, R., Drug dependence.
SOURCEID: Austin, University of Texas Press, 1970. 342 p. (p. 214-226).

A study was undertaken to relate the reinforcing functions of drugs to their potential for physical and/or psychological dependence, to experimentally examine the discriminative functions of drugs and relate them to drug dependent behavior, and to extrapolate from animal based results principles of drug dependent behavior that may be applicable to man. Initially albino rats were trained in operant conditioning chambers to obtain food by pressing levers. Rats were injected with 1.0mg/kg of dl-amphetamine and given 8 days of training in the drug state; tests for discriminative control of responding were carried out in extinction. Results with these and other doses and drugs confirm the discriminative stimulus function of drugs and suggest that a generalization of the effect can occur across drugs of similar central activity. It is suggested that psychological dependence based on the discriminative function of drugs requires drugs that induce distinguishable sensory effects and self-administration of these drugs in chain schedules in which ultimate reinforcement is contingent on the emittance of forms of behavior other than drug consumption. It is postulated that psychological dependence can be viewed as drug self-administration in which drugs function as unconditional reinforcers, conditioned reinforcers or discriminative stimuli. 21 references.

46312
AUTHORS: Wittenborn, J. R.
TRTITLE: /Effects of meprobamate on emotional responses./
TITLE: Animal studies.
SOURCE: In: Wittenborn, J., The response to meprobamate -- a predictive analysis.
SOURCEID: New York, Raven Press, 1970, 113 p. (p. 15-26).

Animal studies of meprobamate are reviewed. The various reports of controlled investigations describing the effect of meprobamate on fighting and related behavior are not altogether consistent in their implications. As a result, the question of the effect of meprobamate on aggression is surrounded with ambiguities and qualifications. In a study wherein fighting was induced in animals by isolation, meprobamate did not appear to have a selective effect, and fighting behavior was suppressed at doses which begin to have a neurological effect. Experiments were conducted on the effect of meprobamate on the emotional responses of animals, particularly fear - like responses; the effect of meprobamate on self-stimulation behavior of rats in which electrodes had been implanted in the hypothalamus; the effect of certain ataraxic agents on the activity of mice; the effect of meprobamate on operant behavior in rats; and the effect of meprobamate on avoidant behavior. Other studies included the pole jumping response as a function of meprobamate dosage; and a y-maze to study the effect of various drugs on exploratory behavior. It was found that meprobamate was accompanied by increases in exploratory behavior which became statistically significant at 200mg/kg.

47323
AUTHORS: Lambert, G. A.; Lang, W. J.
TITLE: The effect of bradykinin and eledoisin injected into the cerebral ventricles of conscious rats.
SOURCE: European Journal of Pharmacology (Amsterdam).
SOURCEID: 9(3):383-386, 1970.

Bradykinin and eledoisin produced a pressor response and behavioral excitation when injected into the cerebral ventricles of

conscious rats with a ventricular cannula modified to include a device for monitoring carotid arterial pressure. The behavioral response to both peptides was abolished after morphine but was not detectably altered by pretreatment with phentolamine or propanolol. The pressor responses to both peptides were prevented by pretreatment of the rats with phentolamine mesylate, but not with propranolol. Pretreatment with morphine prevented the pressor response to bradykinin but not to eledoisin. 12 references. (journal abstract modified)

47324
AUTHORS: Rosecrans, John A.
TITLE: Differences in brain area 5-hydroxytryptamine turnover and rearing behavior in rats and mice of both sexes.
SOURCE: European Journal of Pharmacology (Amsterdam).
SOURCEID: 9(3):379-382, 1970.

Rats and mice of both sexes were compared as to rearing behavior and 5-hydroxytryptamine (5-HT) turnover in forebrain and areas caudal to this. Turnover rates were calculated from changes in 5-HT metabolism in animals pretreated with the monoamine oxidase inhibitor, pargyline (75 mg/kg i.p.). The female rats reared twice as often as the male, and their forebrain steady state 5-hydroxyindoleacetic acid (5-HIAA) levels were significantly elevated. Forebrain and brainstem levels of 5-HIAA and 5-HT are compared between sexes of both species. Results indicate that the female of each species has both a more functional 5-HT system and a higher rate of rearing, interpreted on the basis of data indicating that stimulation of 5-HT systems normally depress the ability of an animal to habituate to a novel environment. 10 references. (journal abstract modified)

47326
AUTHORS: Geller, I.; Blum, K.
TITLE: The effects of 5-HTP on para-chlorophenylalanine (p-CPA) attenuation of "conflict" behavior.
SOURCE: European Journal of Pharmacology (Amsterdam).
SOURCEID: 9(3):319-324, 1970.

The effects of 5-hydroxytryptophan (5-HTP) on para-chlorophenylalanine (p-CPA) attenuation of conflict behavior were studied. Conflict was induced in hungry rats by simultaneously rewarding with food and punishing with shock. The lever responses were made in the presence of a tone stimulus. This procedure resulted in a suppression of responses during tone stimuli. Administration of p-CPA attenuated the conflict and reinstated the suppressed responding, an effect which persisted as long as 2 weeks. A 15mg/kg dose of 5-HTP reversed the para-chlorophenylalanine effects for more than 24 hours; the same dose was without effect when administered to rats in which suppressed responding had been reinstated by lowering shock levels rather than administering p-CPA. The 5-HTP reversal of p-CPA effects on conflict suggests that the p-CPA effects are due to serotonin depletion. 18 references. (journal abstract modified)

40027
AUTHORS: Bakay, Bohdan; Nyhan, William L.
TITLE: Effects of thalidomide and chlorcyclizine on the biosynthesis of nucleic acids and proteins in fetal and maternal tissues of the rat.
SOURCE: Journal of Pharmacology and Experimental Therapeutics.
SOURCEID: 171(1):109-117, 1970.

The effects of the teratogens thalidomide and chlorcyclizine on the biosynthesis of nucleic acids and proteins were studied in pregnant rats. Thalidomide administration resulted in the accumulation of labeled precursors, thymidine and glycine, in the nucleic acids of fetus and maternal tissues, suggesting accelerated biosynthesis of deoxyribonucleic acid and ribonucleic acid. The increase in the accumulation of thymidine was reversed by actinomycin D. Thalidomide had comparatively little effect on the incorporation of precursors into tissue proteins. In contrast, after chlorcyclizine and accumulation of isotopes of thymidine in the fetus was less than in controls. Chlorcyclizine promoted the incorporation of amino acids into the proteins of fetal and maternal tissues. The data suggest a suppression of deoxyribonucleic acid synthesis in the fetus, but a stimulation of the biosynthesis of proteins. 14 references. (author abstract modified)

40028
AUTHORS: Muller, Patricia J.; Vernikos-Danellis, Joan.
TITLE: Effect of environmental temperature on the toxicity of caffeine and dextroamphetamine in mice.
SOURCE: Journal of Pharmacology and Experimental Therapeutics.
SOURCEID: 171(1):153-158, 1970.

The effects of environmental temperature and dehydration, individually and in combination, on the toxicity of caffeine and dextroamphetamine were studied in mice. The LD50 was compared at 22 C, 30 C, and 15 C with and without dehydration. No statistically significant difference in LD50 could be shown between acute (1 hour) and subacute (3 days) preinjection exposures. A 7 to 8 degree alteration in temperature above or below 22 C significantly changed the toxicity of both drugs. At 15 C, the toxicity of dextroamphetamine decreased 10 fold, and the animals were protected from its toxic effects; at 30 C, toxicity increased 2 to 3 fold. Both warming and cooling appeared to increase the toxicity of caffeine. Dehydration caused a marked decrease in the LD50 of both drugs. This decrease was more pronounced at the higher temperatures, with the exception of dextroamphetamine at 15 C where cooling appeared to mask the increase in toxicity otherwise produced by dehydration. The combination of dehydration and change in temperature showed an additive effect on the toxicity of caffeine at 15 C and dextroamphetamine at 30 C, whereas a marked potentiation occurred with caffeine at 30 C. The results indicate that alterations of the environmental temperature affect drug toxicity. These alterations do not have to be particularly drastic, but mild variations in temperature are effective. 35 references. (author abstract modified)

40124
AUTHORS: Bedard, P.; Larochelle, L.; Poirier, L. J.; Sourkes, T. L.
TITLE: Reversible effect of l-dopa on tremor and catatonia induced by alpha-methyl-p-tyrosine.
SOURCE: Canadian Journal of Physiology and Pharmacology (Ottawa).
SOURCEID: 48(1):82-84, 1970.

A study was made of the effect of l-dopa on tremor and catatonia induced by alpha-methyl-p-tyrosine. In 5 monkeys, unilateral lesions were stereotaxically placed in the brain stem or cerebellum in order to interrupt the rubro-olivo-cerebello-rubral loop on one side. In the 5 lesioned animals, dl-alpha-methyl-p-tyrosine (500mg i.p.)

induced postural tremor in corresponding limbs. This effect appeared after a delay of 3 to 4 hours and lasted up to 12 hours. The injection of the same substance (1000-1500mg i.p.) into normal or lesioned monkeys induced catatonia within 24 hours. Tremor and catatonia were repeatedly reversible within 15 minutes by l-dopa (30mg/kg i.m.); the effects reappeared, however, after 45 to 60 minutes. The effects may be related to a decreased concentration of brain catecholamines as a result of the inhibitory effect of this substance on tyrosine hydroxlyase. 9 references.a

40125
AUTHORS: Heikel, T. A. J.; Lathe, G. H.
TITLE: The effect of oral contraceptive steroids on bile secretion and bilirubin Tm in rats.
SOURCE: British Journal of Pharmacology (London).
SOURCEID: 38(3):593-601, 1970.

A study was made of the effect of oral contraceptive steroids on the bile secretion and bilirubin secretion rates in rats. Virgin female Wistar rats weighing 145 to 290 gm were fed rat MRC 41B diet. The rats were not fasted before use. Bilirubin maximum secretion rate was determined according to the technique of Weinbren and Billing (1956). Both 17-alpha-ethinyl substituted estrogens and progestogens greatly reduced the basal bile flow. The parent compounds, estradiol-17-beta and 19-nortestosterone had little or no effect. A much larger dose of progestogens (40mg/kg) than estrogens (5mg/kg) was needed. Between 12 and 48 hours were required for to 17-alpha-ethinylestradiol to produce the effect. Bilirubin maximum secretion rate was little affected, the only significant reduction being produced by the 3-methyl ether of 17-alpha-ethinylestradiol (mestranol). Rises is serum conjugated bilirubin following infusion of bilirubin were produced by 17-alpha-ethinylestradiol and mestranol but not by the progestogens. 22 references.

45543
AUTHORS: Forrest, I. S.; Kosek, J. C.; Aber, B. C.; Serra, M. T.
TITLE: Rabbit as a model for chlorpromazine-induced hyperpigmentation of the skin.
SOURCE: Biochemical Pharmacology.
SOURCEID: 19(3):849-852, 1970.

Hyperpigmentation of exposed skin areas, comparable to that seen in less than 1% of patients chronically dosed with chlorpromazine after intensive long term therapy, was produced in 16 out of 16 chronically dosed pigmented rabbits, receiving between 20mg/kg/day to 30mg/kg/day. Thirty min ultraviolet irradiation of clipped or shaved area produced hyperpigmentation of naturally pigmented skin areas in about 4 weeks. The characteristic occurrence of granular pigment in the dermis which is normally free of pigment was also observed. Previous data suggest that melanin was instrumental in accelerating the oxidation of 7-hydroxychlorpromazine to its positive ion radical which ultimately formed charge transfer complexes with peripheral melanoprotein. Hyperpigmented rabbits did not develop any concomitant ocular pathology, as seen in some patients on long term, high dosage chlorpromazine therapy, indicating that such side effects are not due to the same genetic or metabolic conditions giving rise to hyperpigmentation of the skin. 11 references. (author abstract modified)

46640
AUTHORS: Owen, Gareth; Smith, T. H. F.; Agersborg, H. P. K., Jr.
TITLE: Toxicity of some benzodiazepine compounds with CNS activity.
SOURCE: Toxicology and Applied Pharmacology.
SOURCEID: 16(2):556-570, 1970.

The toxicity is compared of some benzodiazepine compounds with central nervous system activity. Chlordiazepoxide administered

acutely in rodents by oral and intraperitoneal routes was 2 to 3 times as toxic as diazepam, and diazepam was at least 3 times as toxic as oxazepam. Oxazepam produced minimal increase in liver fat in rats, while chlordiazepoxide and diazepam produced increased renal tubular pigmentation. Dogs dosed orally with 60-80mg/kg, 120-127mg/kg or 200-240mg/kg daily for 4 weeks did not die with oxazepam, but 6 died with 200mg/kg chlordiazepoxide and 1 with 200mg/kg diazepam. Sedation was greater with the latter 2 compounds. High serum alkaline phosphatase and/or serum cholesterol occurred in a few dogs treated with 240mg/kg oxazepam, but in nearly all treated with chlordiazepoxide or diazepam, it was accompanied in the latter by elevation of sulfobromophthalein, serum glutamic oxaloacetic transaminase, and serum glutamic pyruvic transaminase and decreased blood sugar. Only slight prostatic atrophy was found with oxazepam. Prostatic and gonadal changes were observed with chlordiazepoxide; liver, renal and gonadal alterations were seen with diazepam. Treatment of male and female parent rats with oxazepam before and throughout 2 mating cycles and female parent rats and rabbits from days 8 to 16 of the gestation period did not produce drug related differences or abnormalities in the offspring. Treatment of parent female mice throughout gestation affected the incidence of stillbirths and decreased pup survival; 7 days premating treatment affected fertility. 1 reference. (author abstract modified)

41537
AUTHORS: Beattie, I. A.; Berry, P. A.; Lister, R. E.
TITLE: Methods for detecting anti-anxiety drugs using baboons (Papio cynocephalus).
SOURCE: British Journal of Pharmacology (London).
SOURCEID: 38(2):460P-461P, 1970.

The spontaneous social behavior in monkey colonies can be modified by the administration of drugs such as pentobarbital, chlorpromazine, Medazepam and chlordiazepoxide. Video tape recorders are used to record the effects of new psychoactive substances, particularly the suppression of aggression induced in the colony leader by introduction into a colony of a stranger, either human or baboon. Medazepam was found to be very effective in reducing anxiety without producing sedation. Pentobarbital and chlorpromazine reduced the incidence of aggression but some sedative effects were observed. 4 references.

45545
AUTHORS: Dairman, Wallace; Balazs, Tibor.
TITLE: Comparison of liver microsome enzyme systems and barbiturate sleep times in rats caged individually or communally.
SOURCE: Biochemical Pharmacology.
SOURCEID: 19(3):951-955, 1970.

Behavioral and physiological changes induced by the prolonged caging of Wistar rats were studied. After 3, 6 and 12 weeks of caging, rats from individual and community cages were examined for the duration of sleep time after the administration of various barbiturates; liver/body weight ratios were determined and at the 3 and 12 week periods, hepatic microsomal enzyme activity in vitro was also determined. Barbituate sleep time was designed as the time interval from the loss to the regaining of the righting reflex. The individually caged rats' sleep times in response to pentobarbital,hexobarbital and barbital were significantly shorter than those of the community caged controls after 3 weeks. In liver homogenates no significant differences were found in the enzyme activities measured or the absolute body, liver, or adrenal weights of the individually and community caged animals. Upon handling, individually caged animals were excitable and intractable by the third week, whereas community caged rats were docile. After 12 weeks there were no statistically significant differences in pentobarbital and hexobarbital sleep times between the 2 groups, but rats individually caged for 12 weeks did show an increased sensitivity to isoproterenol. The data indicate that individually caged rats can partially adapt to their environment but individual caging of rats results in observable behavioral changes and pharmacological responses. 12 references.

07 EARLY CLINICAL DRUG TRIALS

42483
AUTHORS: Mawdsley, C.
TITLE: Treatment of parkinsonism with laevo-dopa.
SOURCE: British Medical Journal (London).
SOURCEID: No. 5692:331-337, 1970.

Thirty two patients with Parkinsonism were treated with L-dopa. Nine were markedly and 14 moderately improved. Twenty patients tolerated the drug well, derived definite improvement, and were treated for an average period of six months. Improvement was sustained during the period even though the average daily dosage of L-dopa was reduced. Dose dependent side-effects occurred in 25 patients. It is suggested that dosage schedules should be flexible and tailored to the needs of each individual patient, and that treatment should be continued for six months before presuming it to be ineffective. It is concluded that L-dopa often ameliorates Parkinsonism for long periods, but its effect on the natural history of the disease is undetermined. 27 references. (author abstract)

42676
AUTHORS: Gayral, Louis; Caussinus, Henri; Schecktman, Y.
TRTITLE: /Statistical method of analysis and evaluation of psychotherapeutic results: application of a long acting neuroleptic, compared with a standard neuroleptic and the Sakel insulin treatment./
TITLE: Methode statistique d'analyse et d'appreciation des resultats therapeutiques en psychiatrie: exemple d'application a un neuroleptique retard et comparaison avec un neuroleptique standard et avec la cure insulinique de Sakel.
SOURCE: Therapie (Paris).
SOURCEID: 25(1):29-42, 1970.

A study of 3 groups of schizophrenic patients treated by either the long acting fluphenazine enanthate (Group I), fluphenazine hydrochloride (Group II), or insulin (Group III) is presented. The results were evaluated by a statistical method, and the criteria used in the evaluation of the patient's condition were the following: the global evaluation; the patient's relationship to hospital clinic (whether in- or outpatient); return to family; return to regular employment; and return to social activity. A chi-squared variant was used in the statistical evaluation. There was no significant difference in results due to sex. The efficacy of the long acting neuroleptic was established in the cases treated. 6 references. (author abstract modified)

45508
AUTHORS: Sletten, Ivan W.; Altman, Harold; El-Toumi, Ashmed; Ognjanov, Vojislav; Watson, Beryl C. E.
TITLE: A double-blind comparision of chlorpromazine and mesoridazine (TPS-23).
SOURCE: Clinical Medicine.
SOURCEID: 77(2):17-20, 1970.

A double-blind comparision study was made of chlorpromazine and mesoridazine on 60 psychotic patients. Thirty received maximal daily doses of 300mg mesoridazine, and 30 received 1000mg chlorpromazine. An item analysis between the predrug ratings and the final ratings on drugs (12 weeks) for both the Brief Psychiatric Rating Scale and the Inpatient Multidimensional Personality Scale showed, for the former, significant improvement on 8 of 16 items for mesoridazine group and no improvement for the chlorpromazine group, and for the latter, equal improvement on 10 items for both drug groups. Minimal side effects included low blood pressure, tremor, rigidity, nausea, blurred vision, acathisia, drowiness and insomnia. No eye changes were noted, and there were no significant ECG findings. Mesoridazine was found to be as effective an antipsychotic drug as chlorpromazine. 12 references.

40127
AUTHORS: Brauzer, Benjamin; Goldstein, Burton J.
TITLE: The differential response to parenteral chlorpromazine and mesoridazine in psychotic patients.
SOURCE: Journal of Clinical Pharmacology and the Journal of New Drugs.
SOURCEID: 10(2):126-131, 1970.

A study was made of the differential response to parenteral chlorpromazine and mesoridazine in psychotic patients. Studied were 40 recently hospitalized psychotic patients who were treated with intramuscular chlorpromazine or mesoridazine in daily doses of up to 225mg over a period of 72 hours. Analysis of covariance revealed significant differences (to the 0.05 level) between the 2 treatments. Mesoridazine more favorably affected the target symptoms of indifference to the environment and conceptual disorganization. Statistical analysis of global improvement, however, showed no significant differences. Drug induced side-effects were transient in nature and mild to moderate in severity. A patient treated with mesoridazine experienced extrapyramidal motor symptoms requiring antiparkinsonian medication. The most frequently occurring side-effects were drowsiness, soreness at the injection site, and hypotension. These occurred in both treatment groups with relatively similar frequency and intensity. A patient treated with mesoridazine experienced a transient cellulitis at an injection site. These results indicate that mesoridazine is at least as effective as chlorpromazine in the same dosage when administered by the parenteral route. 12 references. (author abstract modified)

41568
AUTHORS: Fink, Max; Simeon, Jovan; Itil, Turan M.; Freedman, Alfred M.
TITLE: Clinical antidepressant activity of cyclazocine -- a narcotic antagonist.
SOURCE: Clinical Pharmacology and Therapeutics.
SOURCEID: 11(1):41-48, 1970.

Clinical evaluations of the antidepressant activity of cyclazocine, a narcotic antagonist, were made with chronically mentally ill patients and with depressive ambulatory patients. In both studies a majority of patients benefited from this drug, but secondary effects were common, suggesting a narrow therapeutic range. In the treatment of opiate dependence, elation, insomnia, and increased libido with administration and a "grippe like" syndrome on acute withdrawal were recorded as secondary effects. In the scalp recorded electroencephalogram (EEG), desynchronization, decreased alpha abundance, and increased fast and theta activities were recorded concurrently, indicating similarity to the tricyclic antidepressants. The antidepressant activity does not seem to be related to the antinarcotic activity. 29 references. (author abstract modified)

42654
AUTHORS: Wilson, I. C.; Prange, A. J., Jr.; McClane, T. K.; Rabon, A. M.; Lipton, M. A.
TITLE: Thyroid-hormone enhancement of imipramine in nonretarded depressions.
SOURCE: New England Journal of Medicine.
SOURCEID: 282(19):1063-1067, 1970.

The speed and efficacy of imipramine in the treatment of clinical depression were enhanced by the addition of tri-iodothyronine to the treatment program. L-tri-iodothyronine (25 micrograms daily) added to imipramine (150mg/day) significantly improved performance on the Hamilton Rating Scale and the Self-rating Depression Scale as compared to that in patients receiving imipramine and a placebo. Morbidity and duration of hospitalization were diminished. The patients were euthyroid according to conventional clinical and laboratory criteria. The hormone quickened ankle reflex time and suppressed levels of protein bound iodine. These physiologic changes, though not definite, were slight and within the limits of euthyroidism as usually defined. 24 references. (author abstract)

42671
AUTHORS: Ravn, Jorgen.
TRTITLE: /Ten years of treatment with thioxanthene derivatives./
TITLE: 10 Jahre Behandlung mit Thioxanthenderivaten.
SOURCE: Medizinische Welt (Stuttgart).
SOURCEID: 21(7):275-279, 1970.

Ten years' experience with the thioxanthene derivatives, chlorprothixene, chlopenthixol, and flupenthixol (individually or in combination with other drugs) in treating patients with acute psychoses is presented. No matter what the etiology, the long-term treatment gave excellent results. In addition, the preparations were also used successfully in the treatment of chronic psychoses for both in- and outpatients. The tolerance was found to be excellent, and particularly valuable in long-term treatment. These derivatives are therefore highly recommended as antipsychotic agents. 30 references. (author abstract modified)

47828
AUTHORS: Baer, Leslie; Durell, Jack; Bunney, William E.; Levy, Bernard S.; Murphy, Dennis L.; Greenspan, Kenneth; Cardon,

P. V.
TITLE: Sodium balance and distribution in lithium carbonate therapy.
SOURCE: Archives of General Psychiatry.
SOURCEID: 22(1):40-44, 1970.

The effect of lithium carbonate administration on 24-hour exchangeable sodium (NaE), sodium space (Na), extracellular fluid (ECF) volume, and residual sodium (NaR) was studied in 11 patients with affective disorders, primarily manic-depressive disease. Lithium carbonate administration was associated with a significant increase in 24-hour Na space in the entire group of patients and there was a trend for the ECF volume to increase and the NaR to decrease. The patients who responded clinically to lithium carbonate had a significantly greater increase in 24-hour NaE when compared to the nonresponders. No differences were noted between manic and nonmanic patients. The observed electrolyte changes suggest that one action of the lithium ion may involve altered Na metabolism. 17 references. (author abstract)

47831
AUTHORS: Baldessarini, Ross J.; Stephens, Joseph H.
TITLE: Lithium carbonate for affective disorders. I. Clinical pharmacology and toxicology.
SOURCE: Archives of General Psychiatry.
SOURCEID: 22(1):72-77, 1970.

The clinical pharmacologic and toxicologic experience at the Henry Phipps Psychiatric Clinic with lithium carbonate therapy with 62 patients during the past year is reported. Oral dose:blood concentration correlations were predictable and stable over time. Untoward effects were rare and for the most part, inconsequential. There was one instance of myocardial infarction and another of grand mal seizure. In neither case were either the dosage or serum concentration of lithium high. There were 4 cases of edema, most of which occurred in patients receiving thioridazine as well as lithium carbonate. The present findings support the conclusion of those who have worked extensively with lithium salts in Europe and Australia that these salts can be quite safe even for outpatients when adequate control of the serum lithium concentration is established and pursued. Certain dangers in the use of drugs with small toxicity:efficacy dosage ratios are pointed out. These can be reduced by selecting reliable patients, and discouraging abuses by close and regular medical supervision, which should include periodic blood assays of the drug or its metabolites. Evidence of alterations in lithium metabolism with affective status was not found. 30 references. (author abstract)

47919
AUTHORS: Lipkin, K. Michael; Dyrud, Jarl; Meyer, George G.
TITLE: The many faces of mania: therapeutic trial of lithium carbonate.
SOURCE: Archives of General Psychiatry.
SOURCEID: 22(3):262-267, 1970.

A series of cases is presented to call attention to certain acute manic episodes which masquerade as paranoid or schizophrenic reactions. A prompt response to lithium carbonate was observed in these cases as well as practical difficulties in maintaining prophylactic treatment. The differential diagnosis of mania is reviewed. With proper safeguards and investigational intent a therapeutic trial of lithium carbonate seems warranted in such cases. 17 references. (author abstract)

47951
AUTHORS: Curry, Stephen H.; Marshall, John H. L.; Davis, John M.; Janowsky, David S.
TITLE: Chlorpromazine plasma levels and effects.

SOURCE: Archives of General Psychiatry.
SOURCEID: 22(4):289-296, 1970.

Following acute doses of chlorpromazine, psychiatric patients showed sedation for the duration of elevated plasma levels of the drug. Chronic treatment of the same patients resulted in stabilization at higher plasma levels and no sedation, but sedation could then be induced by a further increase in the dose and levels. Hypotensive effects were confined to the early stages of treatment, and individual patient sensitivity varied greatly, although effects were greatest at highest plasma levels. Psychopharmacological effects, both desirable and undesirable, were observed only in chronically treated patients, and, again, individual patient sensitivity varied considerably, In particular, an adverse psychotic reaction was observed in a patient with very high levels and considerable improvement resulted from reduction of these levels, suggesting that poor chlorpromazine response may be caused by either low or excessively high levels. 33 references. (author abstract)

47952
AUTHORS: Platman, S. R.; Fieve, R. R.; Pierson, R. N., Jr.
TITLE: Effect of mood and lithium carbonate on total body potassium.
SOURCE: Archives of General Psychiatry.
SOURCEID: 22(4):297-300, 1970.

Neither the manic nor the depressive phases of manic -depressive psychosis are associated with a substantial change in TBK (total body potassium); in 26 patients, all but 3 fell within 1 standard deviation of the mean measurement of an appropriately selected normal group. Lithium carbonate, in the doses used, resulted in no consistent change in TBK. 7 references. (author abstract)

47953
AUTHORS: Kerry, Raphael J.; Owen, Goronwy.
TITLE: Lithium carbonate as a mood and total body water stabilizer.
SOURCE: Archives of General Psychiatry.
SOURCEID: 22(4):301-303, 1970.

The greater variability of mood and total body water (TBW) in manic - depressive illness is discussed in relation to a group of normal controls. Three cases studied over 5 years suggest that daily doses of lithium carbonate may prevent both large mood and TBW changes in at least some manic -depressive subjects. The need for further long term study is stressed. 7 references. (author abstract)

47954
AUTHORS: Sachar, Edward J.; Hellman, Leon; Kream, Jacob; Fukushima, David K.; Gallagher, Thomas F.
TITLE: Effect of lithium-carbonate therapy on adrenocortical activity.
SOURCE: Archives of General Psychiatry.
SOURCEID: 22(4):304-307, 1970.

Cortisol production rates, endogenous production of cortisol metabolites, and plasma cortisol levels were determined in 7 patients with recurrent affective disorders before and during lithium carbonate therapy. In 3 additional patients plasma cortisol levels alone were examined. No significant change in adrenocortical activity was found. It is concluded that the prophylactic action of lithium ion in manicdepressive illness does not involve secretion of cortisol. 10 references. (author abstract)

47836
AUTHORS: McNair, Douglas M.; Fisher, Seymour; Kahn, Richard J.; Droppleman, Leo F.
TITLE: Drug-personality interaction in intensive outpatient treatment.
SOURCE: Archives of General Psychiatry.
SOURCEID: 22(2):128-135, 1970.

This report presents the rationale, experimental design, and methodology for a double - blind controlled outpatient drug study. The experimental hypothesis predicted that an interaction between degree of patient acquiescence and medication markedly affects the patient's clinical response to mild tranquilizers and placebo. Eight female patients completed a total of 488 phase 2 study days. The results confirmed the experimental hypotheses and replicated earlier findings on a larger group. With a different mild tranquilizer, the same personality medication interaction appeared. Low acquiescent patients reported less anxiety on drug days than on placebo days. For low acquiescers, tension anxiety decreased the longer they remained on drug (up to 7 days), and their level of anxiety increased the longer they remained on placebo. Low acquiescers reported some increased sedation fatigue the first day on drug in each cycle, but there was no evidence that this persisted. High acquiescers reported no antianxiety effects of the drug. In fact, for high acquiescers, tension anxiety increased with duration of the drug cycle. Similarly to low acquiescers, the high acquiescers reported increased sedation fatigue on the first day of drug cycles. With high acquiescers, however, this effect persisted for 4 days before dissipating. This "clearing" of sedation fatigue effects in high acquiescers appeared to have a puzzling coincidence with increased tension anxiety. The results support an earlier recommendation that level of acquiescence be considered in the methodology of outpatient drug trials. Failure to consider this characteristic could easily make it difficult to detect an effective drug for low acquiescers. Further understanding is needed of the relationship of acquiescence to both favorable and adverse reactions to drugs, and some studies are in progress. 13 references. (author abstract modified)

42693
AUTHORS: Czerwenka-W., H.; Maly, J.; Quatember, R.; Tschabitscher, H.
TRTITLE: /Clinical and psychological testing of a geriatric drug./
TITLE: Klinische und testpsychologische Untersuchungen mit einem Geriatricum.
SOURCE: Wiener Medizinische Wochenschrift (Vienna).
SOURCEID: 120(13):217-224, 1970.

A double-blind study in 232 patients, testing the efficacy of the geriatric drug KH-3, a procaine derivative, is presented. Along with the clinical investigation, a battery of 7 objective tests by a projective method and a standard interview were included. The results which were processed by a high speed computer analyzer revealed statistically significant improvement (at the 1% level) in mental performance, in visual - motor coordination and in perception, drive and alertness. There was improvement (at the 5% level) in the depressive symptoms, although it was not possible to distinguish endogenous from exogenous depression. Some of the other improvements are connected with activity and lessening of fatigue and are discussed in terms of the findings of other investigators. 33 references. (author abstract modified)

42700
AUTHORS: Olesen, O. Vendelin; Jensen, O. Nygaard.
TITLE: Subnormal serum folate due to anticonvulsive therapy: a double-blind study of the effect of folic acid treatment in patients with drug-induced subnormal serum folates.
SOURCE: Archives of Neurology.
SOURCEID: 22(2):181-182, 1970.

In a double-blind crossover study, 24 patients suffering from epilepsy and with drug induced subnormal serum folate (SF) were treated with folic acid (20mg/day) through 5 months in order to evaluate the effect of folic acid administration on the mental state, fit frequency, hematological condition, and serum levels of diphenylhydantoin and phenobarbital. With the exception of a slight decrease in serum diphenylhydantoin levels, no changes that could be ascribed to folic acid treatment were observed. It is concluded that drug induced subnormal SF as the sole abnormal manifestation of a folate deficiency is of no clinical importance. 6 references. (author abstract)

43697
AUTHORS: Parkes, J. D.; Zilkha, K. J.; Calver, D. M.; Knill-Jones, R. P.
TITLE: Controlled trial of amantadine hydrochloride in Parkinson's disease.
SOURCE: Lancet.
SOURCEID: No. 7641:259-262, 1970.

Thirty seven outpatients with Parkinson's disease were treated for 2 weeks with daily doses of 200mg of amantadine hydrochloride and placebo in a double-blind crossover trial. Thirty five of the patients reported a preference for amantadine therapy. All features of history and clinical examination showed improvement of scores on amantadine except for the patients' assessment of their walking ability and the observer's examination of rigidity. The degree of improvement was not related to age, sex, duration or severity of disease, previous thalamolysis or concomitant medication. Amantadine hydrochloride is similar in mode of action to L-dopa, with fewer side effects, but with less efficacy. 12 references.

46315
AUTHORS: Wittenborn, J. R.
TITLE: Controlled studies of therapeutic effect.

SOURCE: In: Wittenborn, J., The response to meprobamate --a predictive analysis.
SOURCEID: New York, Raven Press, 1970. 113 p. (p. 39-73).

Controlled studies of the therapeutic effect of meprobamate are reviewed. The premise that meprobamate ameliorates behavioral difficulties by reducing acquired avoidant reactions may illuminate the conditions under which and the individuals for whom meprobamate is an effective medication. This review is limited to those studies which involve the principle of controlled comparisons and which describe therapeutic effects with sufficient clarity to make replication possible. The material is organized on the basis of several substantive topics pertinent to familiar areas of clinical application. The topics discussed are geriatric patients, stutterers, nonpsychiatric patients, children, alcoholics, anxiety and related states among outpatients, psychiatric inpatients, and dosage considerations.

46316
AUTHORS: Wittenborn, J. R.
TITLE: Studies with qualified or negative implications.
SOURCE: In: Wittenborn, J., The response to meprobamate -- a predictive analysis.
SOURCEID: New York, Raven Press, 1970. 113 p. (p. 74-87).

Available reports which fail to confirm the expected indications of efficacy for meprobamate are examined. Conditions which do not yield in response to meprobamate are identified, and the extent to which the failures in meprobamate effect are consistent with previous hypotheses are assessed. Upon close examination, most of the studies reviewed were found to be ambiguous with respect to the question of efficacy per se.

46733
AUTHORS: Cohen, Sidney.
TITLE: Psychotherapy with LSD: pro and con.
SOURCE: In: Cohen, S., The beyond within: the LSD story.
SOURCEID: 2nd ed. New York, Atheneum, 1970. 312 p. (p. 180-207).

A description of the psychotherapy process is given in general terms, concluding with a list of 17 goals, also cast in general terms. Some comparisons between brainwashing and psychotherapy are given. Proponents of the use of hallucinogens in psychotherapy claim reduced defensiveness, better recall, detachment, and confidence in the therapists, coupled with alertness and insight retention. There is a marked increase in suggestibility. Use of lysergic acid diethylamide (LSD) under well prepared and controlled conditions provides rapid and enormous insights. However, LSD does not shorten the laborious process of relearning. The conditions and preparation for effective use of LSD are described. Types of patients suited and unsuited for LSD treatment are discussed, as is group therapy. Effects on chronic alcoholics are described in detail, with commentary on rapid personality conversion. 1 reference.

47825
AUTHORS: Smith, Burke M.; Hain, Jack D.; Stevenson, Ian.
TITLE: Controlled interviews using drugs.
SOURCE: Archives of General Psychiatry.
SOURCEID: 22(1):2-10, 1970.

Under triple-blind conditions, 49 psychiatric patients were interviewed about their illnesses and life experiences after administration of one of four randomly selected drugs, amobarbital, metamphetamine, hydroxydione and saline. The interviewers and observers, blind to the drug given, rated the behavior of the patient and interviewer (on a variety of behavioral items) during the interview. Analysis of the results obtained showed that symptomatic changes in the patients' conditions 24 hours after the interview were

not related to emotional expression during the interviews when saline, hydroxydione and amobarbital were given. When methamphetamine was the drug given, a relation occurred between the expression of elation during the interviews and symptomatic change 24 hours after the interviews. Since the patients, during the interviews, were reviewing earlier events of their lives which had been mostly unpleasant for them at the time of their occurrence, the expression of an unpleasant affect in reliving or recounting memories of previous events is not a requirement for symptomatic change after the interview. Hydroxydione was accompanied by the least anxiety during the interviews. Since anxiety during the retelling of past experiences is not a requirement for improvement, and may inhibit the patient's expression, hydroxydione deserves further investigation for its possible value in psychiatric interviewing. Hydroxydione has the additional advantage over amobarbital of being rapidly metabolized. Interviewer influence on the results of drug interviews will be considerably greater in uncontrolled interviews than it was shown to be in the present controlled series. It is therefore important to allow for this factor in interpreting results reported from uncontrolled series of drug interviews. 27 references. (author abstract modified)

12 PSYCHOTOMIMETIC EVALUATION STUDIES

46725
AUTHORS: Cohen, Sidney.
TITLE: The beyond within: the LSD story.
SOURCEID: 2nd ed. New York, Atheneum, 1970. 312 p. $6.95.

On the basis of extensive experience with lysergic acid diethylamide (LSD) under hospital conditions in a program of scientific research, the effects of LSD on a number of subjects are recounted. The potentials of LSD in tapping the subconscious or abnormal mind are discussed, and the usefulness of the results to therapists is outlined. Mystical and visionary experiences are discussed in relation to what has been learned from the hallucinogens. Possible military uses of these drugs are described. Latter day use of LSD as a sacrament in a neoreligion and by acid heads for kicks are examined from a sociological point of view. A brief section on the chemistry of the hallucinogens is included. 20 references.

46727
AUTHORS: Cohen, Sidney.
TITLE: The research.
SOURCE: In: Cohen, S., The beyond within: the LSD story.
SOURCEID: 2nd ed. New York, Atheneum, 1970. 312 p. (p. 32-44).

The animal pharmacology and human pharmacology and psychology of lysergic acid diethylamide (LSD) are discussed. Experiments with animals have produced no sensational reactions; a number of specific reactions are described. The infinitesimal amount of the drug necessary to produce a reaction in humans is noted, together with the onset and duration of symptoms. Very little LSD remains in the brain. The diencephalon is the locusof the extraordinary reactions. There is a rapid onset of tolerance. Tranquilizers are excellent antidotes. Bodily changes are minor, and unpleasant physical side-effects are limited. Psychological effects include changes in time perception, decreased sensitivity to pain, decreased intellectual functioning, and dissolution of ego boundaries. There is a disinhibiting action on learned patterns, particularly those related to reality testing, survival functioning, goal directed behavior, and logical thinking. 2 references.

46728
AUTHORS: Cohen, Sidney.
TITLE: Seeing with all three eyes.
SOURCE: In: Cohen, S., The beyond within: the LSD story.
SOURCEID: 2nd ed. New York, Atheneum, 1970. 312 p. (p. 45-63).

An extended discussion of normal perception and consciousness is given which demonstrates a wide variety of normality, degrees of acceptance of conventions, and the fact of rapid visual readjustments. The perceptual apparatus focuses on the new and unexpected. One of the unique qualities of lysergic acid diethylamide (LSD) is its capacity to temporarily recapture the vividness of newness and to convert perception into an end in itself. LSD also heightens sensitivity of hearing and touch, but has relatively little effect on taste and smell. Synesthesia is also frequent. Hallucinogenic and other results of sensory deprivation experiments are discussed, including those involving the use of LSD. The exploration of the human mind's still unknown potential should involve controlled experiments with the hallucinogenic state. The concept of a linear bipolarity of sanity and insanity should be revised to facilitate such exploration. A horseshoe shaped concept of mental activity is suggested, with unsanity and insanity at the tips, both in the unconscious state, and sanity at the base in the conscious segment. 1 reference.

46730
AUTHORS: Cohen, Sidney.
TITLE: Model psychosis or instant zen.
SOURCE: In: Cohen, S., The beyond within: the LSD story.
SOURCEID: 2nd ed. New York, Atheneum, 1970. 312 p. (p. 83-103).

The medical controversy over whether or not lysergic acid diethylamide (LSD) produces a schizophrenic or a visionary state is discussed, and the answer is given that it may produce either or both. The conditions under which the drug is given and the makeup of the individual receiving it are crucial for determination of the direction of the reaction. The psychological phenomena of the schizophrenic state are examined in detail for purposes of comparison. The nature of the visionary experience is reviewed, and its relationships with the LSD state are examined. A theory of the psychological basis of the visionary state is proposed which differentiates it from chemically induced reactions. 2 references.

46731
AUTHORS: Cohen, Sidney.
TITLE: Debriefings.
SOURCE: In: Cohen, S., The beyond within: the LSD story.
SOURCEID: 2nd ed. New York, Atheneum, 1970. 312 p. (p. 104-146).

Excerpts from the written reports of 7 people given LSD under controlled conditions are presented in detail. The experiences described varied according to the personality of the individual, his current life situation, and other factors. The attitude of those in contact with him during the experience, the setting, and the reasons why the drug was given were standardized. Volunteers included doctors, nurses, psychologists, secretaries, businessmen, housewives, and teachers. A series of psychological tests were given before and during the experiment. Motives for volunteering included curiosity, desire for greater self-knowledge, and a desire among the professionals to understand what their patients were feeling. The accounts written shortly after conclusion of the tests range through the full scale of emotions, from utter panic to complete peace.

46732
AUTHORS: Cohen, Sidney.
TITLE: All is as new.
SOURCE: In: Cohen, S., The beyond within: the LSD story.
SOURCEID: 2nd ed. New York, Atheneum, 1970. 312 p. (p. 147-179).

Excerpts from the written reports of 7 people given lysergic acid diethylamide (LSD) under a variety of environments and for a variety of purposes are presented in detail. Some were patients in a study of the drug's therapeutic potential, others were gifted individuals whose creative capacities were being considered. The

situation was less fixed than with a previous set of volunteers, and the investigators were more sympathetic and understanding. Intensity of impressions, extreme simplicity or complexity of consciousness, sense of spatial and temporal discreteness yet relatedness, and singular ego changes are described in the reports. These changes, occurring within a matrix of uncritical acceptance, have a tremendous impact. Some subjects reject them as illusory or psychotic, others accept them as having a meaning beyond ordinary understanding.

47832
AUTHORS: Waskow, Irene E.; Olsson, James E.; Salzman, Carl; Katz, Martin M.
TITLE: Psychological effects of tetrahydrocannabinol.
SOURCE: Archives of General Psychiatry.
SOURCEID: 22(2):97-107, 1970.

Twenty milligrams of trans - tetrahydrocannabinol, when administered to prisoner subjects in a neutral, controlled setting, resulted in a number of subjective effects. Drug subjects, as compared to placebo controls, tended to feel considerable somatic discomfort, some feelings of dizziness and weirdness, and being in a dreamlike floating state. They also reported feeling sleepy and "high." They felt that they were cognitively impaired, that they had experienced some visual changes, and that their time sense was altered. Changes were also obtained on several physiological measures, with drug subjects showing an increased pulse rate, a slight but consistent drop in temperature, and a small drop in blood pressure. Several simple cognitive measures revealed little or no difference due to drug per se. Many of the subjective effects were similar to those commonly attributed to marihuana. A major difference between the subjective effects in this study and those in previous studies of marihuana and THC was in the comparatively minor role played by feelings of elation and euphoria in the present study. Some of the variables that might account for this difference were considered, including subject population, nature of THC as compared to natural marihuana, subject expectations and drug history, and individual differences in personality and physiology. The setting variable investigated in the present study--the use of music--did not result in any significant effects. 19 references. (author abstract)

40105
AUTHORS: Vogel, W. H.; McFarland, H.; Prince, L. N.
TITLE: Decarboxylation of 3,4-dihydroxyphenylalanine in various human adult and fetal tissues.
SOURCE: Biochemical Pharmacology (London).
SOURCEID: 19(2):618-620, 1970.

A study was made of the decarboxylation of dopa (3,4-dihydroxyphenylalanine) by aromatic amino acid decarboxylase in various human adult and fetal tissues, as compared with animal tissues, with and without the addition of codecarboxylase. The decarboxylation of dopa was determined by measuring the formation of (14)CO2 from dopa-1-(14)CO. The extremely low activities of aromatic amino acid decarboxylase found in human brain samples are in agreement with previous results. A comparison of the activities of this enzyme with those of tyrosine hydroxylase, which is the rate limiting step in the biosynthesis of norepinephrine in animal tissues, suggests that perhaps biogenic amine synthesis in human brain tissue is controlled by both tyrosine hydroxylase and aromatic amino decarboxylase. The addition of codecarboxylase increased dopa decarboxylation. Fetal activities were usually higher than those found in adult tissues, except in the heart and brain. This seems to be in contrast with the development of the activity of aromatic amino acid decarboxylase in animal tissues. 14 references.

40573
AUTHORS: Campbell, Iain C.; Todrick, Archibald.
TITLE: Plasma protein binding of tricyclic antidepressive drugs.
SOURCE: Journal of Pharmacy and Pharmacology (London).
SOURCEID: 22(3):226-227, 1970.

The plasma protein binding of tricyclic antidepressive drugs was studied. The effects of imipramine, chlorimipramine, desipramine, and trimipramine upon the uptake of 5-hydroxytryptamine (5-HT) by human blood platelets was determined in plasma and in protein free physiological medium. Platelets in the protein free medium were found to be more sensitive to the inhibiting action of the drugs than those in plasma. A 400 fold range in inhibitory potency was found in this group of drugs, but only a 3 fold range in assessed percentage of free drug. It is concluded that the differences in potency of these drugs depend more on their individual molecular structure than on their degree of binding to circulating proteins. 7 references.

41559
AUTHORS: Hollister, Leo E.; Curry, Stephen H.; Derr, Julia E.; Kanter, Saul L.
TITLE: Studies of delayed-action medication: V. plasma levels and urinary excretion of four different dosage forms of chlorpromazine.
SOURCE: Clinical Pharmacology and Therapeutics.
SOURCEID: 11(1):49-59, 1970.

A study was made of the physiological availability of 4 dosage forms of chlorpromazine. Of the oral forms, liquid or tablets were more reliable than the long acting capsule forms; intramuscular injection of the drug, even in much lower concentrations than the oral forms, led to rapid and regular appearance of significant plasma levels and a consistently higher percent of the administered drug in the urine. 11 references. (author abstract modified)

42756
AUTHORS: Consolo, S.; Morselli, P. L.; Zaccala, M., Garattini, S.
TITLE: Delayed absorption of phenylbutazone caused by desmethylimipramine in humans.
SOURCE: European Journal of Pharmacology (Amsterdam).
SOURCEID: 10(2):239-242, 1970.

The effect of desmethylimipramine (DMI) on the absorption of orally administered phenylbutazone was studied in human subjects. A single pretreatment with 50mg of DMI delayed the time to peak absorption of phenylbutazone in 4 volunteer subjects. Peak phenylbutazone plasma levels in untreated subjects were reached 2-6 hrs after oral phenylbutazone administration, while peaks were not attained even 10 hrs after DMI treatment. A 7 day chronic pretreatment with DMI (25mg 3 times daily) delayed time to peak absorption of phenylbutazone in 4 chronically depressed females from 2 hrs (before DMI) to 4-10 hrs when phenylbutazone was administered 30 min after the last dose of DMI. When phenylbutazone was given 14 hrs after the last dose of a 10 day chronic treatment with DMI (25mg 3 times daily) to another group of 4 females, no clear effect on the time to peak absorption was observed, although plasma levels of phenylbutazone werelower in all 4 patients. The individual differences in phenylbutazone plasma levels may be due to individual variations in the metabolism of DMI. 8 references. (author abstract modified)

46113
AUTHORS: Jaffee, Jerome H.; Anslinger, Harry J.; Tompkins, William F.
TITLE: Physiological effects of marijuana.
SOURCE: In: Goode, E., Marijuana.
SOURCEID: New York, Atherton Press, 1970. 197 p. (p. 43-60).

The physiological effects of marihuana are discussed. When the drug is taken by inhalation of its smoke, effects occur within a few minutes and the duration of the effects is relatively short. After ingestion, usually of the more purified resin, .5 to 1 hour may elapse before onset of effects, and the influence may persist for 3 to 5 hours. There are no lasting ill effects from the acute use of marihuana, and no fatalities have ever been reported. On smoking the drug, there is usually an increase in pulse rate, a slight rise in blood pressure, and conjunctival vascular congestion; blood sugar is slightly elevated; there is urinary frequency without diuresis; dryness of the mouth and throat as well as nausea, vomiting, and occasional diarrhea have also been noted. Various subjective psychological reactions are described. A smoker's view and a policeman's view are also given. 13 references.

46138
AUTHORS: Curry, Stephen H.
TITLE: Plasma protein binding of chlorpromazine.
SOURCE: Journal of Pharmacy and Pharmacology (London).
SOURCEID: 22(3):193-197, 1970.

Plasma protein binding of chlorpromazine was studied in an assessment of the significance of its concentration in plasma. More than 90% of the plasma content of chlorpromazine over a concentration range from 0.008-15.1mcg/ml was found to be bound to human plasma protein. Binding was affected by the pH of the aqueous medium; with few exceptions the higher values were obtained at the higher pH values. Binding was highest in some of the plasma samples from humans, and successively lower in plasma from dogs, rabbits and rats. Binding of chlorpromazine after administration of the drug to psychiatric patients, and after in vitro addition of the drug to plasma, was reversible. Variation in binding in plasma from different humans was marked; the amount bound varied from 91.0% to 99.0%. Thus, the variation in the amount free was from 1.0% to 9.0%. 5 references. (author abstract modified)

46187
AUTHORS: Saggers, V. H.; Hariratnajothi, N.; McLean, A. E. M.
TITLE: The effect of diet and phenobarbitone on quinine metabolism in the rat and in man.
SOURCE: Biochemical Pharmacology (Oxford).

SOURCEID: 19(2):499-503, 1970.

The effect of diet and phenobarbital on quinine metabolism is investigated in the rat and in man. Quinine is metabolized by rat liver microsomes; the microsomes require a nicotinamide - adenine dinucleotide phosphate generating system and their activity is totally inhibited in a gas phase of carbon monoxide. The activity is increased by phenobarbital treatment and decreased by low protein diet. Plasma clearance of quinine in the rat is also increased by phenobarbital treatment and decreased by feeding a purified protein free diet. Human liver metabolizes quinine in the microsomal fraction, but the plasma clearance of quinine in vivo is only slightly altered by phenobarbital in the dosage of 125mg/day for 3 days. 5 references. (author abstract modified)

46195
AUTHORS: Archer, Sydney; Rees, Roberts M.
TITLE: Narcotic antagonists and the problems of drug dependence.
SOURCE: In: Harris, R., Drug dependence.
SOURCEID: Austin, University of Texas Press, 1970. 342 p. (p. 3-12).

Narcotic antagonists are studied because many are clinically effective analgesics and because 2 of them show promise in the management of opiate dependence. Chemical formulas are presented for pentazocine, nalorphine, cyclazocine, and naloxone, and the action of each is discussed and compared with that of the others. Naloxone reverses the agonistic effects of other opioid antagonists and has not produced withdrawal symptoms after chronic administration. Chronic parenteral administration of nalorphine and cyclazocine produces a mild dependence and an analgesic effect. Pentazocine, also an opioid antagonist withoutdependence liability when used under careful medical supervision, has enjoyed the widest clinical use. Pentazocine must be recognized as a potent central nervous system agent that may produce some dependence if used improperly. 16 references. (author abstract modified)

46202
AUTHORS: Hollister, Leo E.
TITLE: Human pharmacology of marihuana (cannabis).
SOURCE: In: Harris, R., Drug dependence.
SOURCEID: Austin, University of Texas Press, 1970. 342 p. (p. 67-79).

The human pharmacology of marihuana (cannabis) is discussed. Various isomers of tetrahydrocannabinol (THC) are believed to account for the major pharmacological activity of cannabis extracts, but some observers believe that crude extracts of cannabis have more clinical effects than can be accounted for by their THC content alone. Nothing is known of the pharmacokinetics of THC, but the potency of THC smoked is 2.5 to 3 times that of the same dose given orally. Cannabis derivatives are remarkably nontoxic. Pharmacological effects in animals include ataxia in dogs, catalepsy, and corneal areflexia in rabbits. A table of major somatic, perceptual, and psychic symptoms in man and a table of changes in Clyde mood scale factors are presented. Physiological and psychological effects of cannabis in man are described, and a table compares pharmacological, physiological, and biochemical effects in animals and men. The social use and therapeutic aspects of marihuana are discussed. 27 references.

46203
AUTHORS: Villarreal, Julian E.
TITLE: Recent advances in the pharmacology of morphine-like drugs.
SOURCE: In: Harris, R., Drug dependence.
SOURCEID: Austin, University of Texas Press, 1970. 342 p. (p. 83-116).

The history of and the recent advances in the pharmacology of morphinelike drugs are discussed. Chemical and pharmacological

properties of a number of morphine derivatives and synthetic morphinelike chemicals are revieved. There is a close but not absolute parallelism of physical dependence production and analgesic activity, except in those compounds such as levomelazocine that exhibit narcotic antagonist properties. It is suggested that all narcotic analgesics share a common receptor mechanism for analgesia, as well as for physical dependence production and for their actions on the central nervous system. The role of N-allyl-normorphine (nalorphine) in the search for a narcotic antagonist is discussed, and opposing theories of the mode of action of nalorphinelike drugs are presented. Studies of the physical dependence capacity of nalorphine, levallorphan, cyclazocine, and pentazocine are reviewed. Benzomorphine isomers with N-methyl substitutes and profadol were studied for their mixed agonist and antagonist properties. Levo-metazocine, GPA-1657, and profadol all possess morphine - antagonist properties, in spite of which 2 of them suppress morphine abstinence in man and all 3 produce significant morphinelike physical dependnece in man. Thus the presence of antagonist properties is no safeguard against physical dependence. 84 references.

47913
AUTHORS: Curry, Stephen H.; Davis, John M.; Janowsky, David S.; Marshall,John H. L.
TITLE: Factors affecting chlorpromazine plasma levels in psychiatric patients.
SOURCE: Archives of General Psychiatry.
SOURCEID: 22(3):209-215, 1970.

Plasma levels of chlorpromazine in a group of psychiatric patients were measured by a new gas - chromatographic technique. Positive identification and quantitative assay of the drug were possible. Plasma levels were compared after administration of chlorpromazine by means of a variety of dosage routes and forms. Levels were highest after intravenous administration, and successively lower levels were recorded after intramuscular doses and oral doses in liquid, tablet, and sustained-release capsule preparations. In all cases, the level rose rapidly after the dose, reaching a peak in 2 to 4 hours and declining to the predosage level within 12 hours. The level at this time was usually less than 20% of the peak level. Studies of urinary and fecal excretion of chlorpromazine showed that the decline of the plasma level results from metabolism of the drug rather than from excretion of the unmetabolized parent compound. 21 references. (author abstract)

40128
AUTHORS: Hollister, Leo E.; Gillespie, H. K.
TITLE: A new stimulant, prolintane hydrochloride, compared with dextroamphetamine in fatigued volunteers.
SOURCE: Journal of Clinical Pharmacology and the Journal of New Drugs.
SOURCEID: 10(2):103-109, 1970.

A comparative study was made of the effects of prolintane hydrochloride and dextroamphetamine in fatigued volunteers. The study involved 24 individuals, 17 males and 7 females ranging in age from 17 to 53 years, who were selected from working persons, preferably on the night shift. Those not working at night were advised to stay awake throughout the night prior to each test period, so as to enter the tests in a fatigued state. Prolintane was administered in doses of 10mg and 20mg; dextroamphetamine, at a dose of 10mg; a placebo was also given. The following observations were made: the Clyde Mood Scale, Number Facility and Flexibility of Closure tests; blood pressure and finger ergograph measurements; and blood samples. Compared to placebo, dextroamphetamine had definite stimulant, euphoriant, anorexiant, and sympathomimetic clinical effects. The larger dose of prolintane had similar effects, but to a lesser degree. 6 references.

40149
AUTHORS: no author.
TITLE: Marijuana program advances at NIMH.
SOURCE: Chemical & Engineering News.
SOURCEID: 48(28):30-33, 1970.

A summary is presented of the comprehensive research effort being conducted at the National Institute of Mental Health aimed at determining whether marihuana is harmful to man. The structure of the active constituents of marihuana and their metabolites, the botanical aspects, and the pharmacological activities of marihuana are being studied.

41562
AUTHORS: Safer, Daniel J.
TITLE: The effect of heat, cold, and work on the central actions of scopolamine.
SOURCE: Clinical Pharmacology and Therapeutics.
SOURCEID: 11(1):60-67, 1970.

Using 48 health, male volunteers, a study was made of the effect of heat, cold and work, in various controlled combinations, on the central actions of scopolamine. The results indicated that mental and motor impairments induced by a low deliriant dose of the drug were significantly increased in ambient temperatures of 95 F and 105 F. Work increased the psychotomimetic effects of scopolamine at 95 F, the highest temperature tested with a drug - and - work group. An increase in peripheral blood flow induced by the drug was most apparent at temperature extremes. 14 references. (author abstract modified)

46199
AUTHORS: Joffe, Milton H.
TITLE: Behavioral effects of STP.
SOURCE: In: Harris, R., Drug dependence.
SOURCEID: Austin, University of Texas Press, 1970. 342 p. (p. 36-40).

The behavioral effects of 2,5-dimethoxy-4-methylamphetamine (DOM, STP) are discussed. Various studies of the effect of DOM on humans and a chimpanzee are reported. Physiological changes and changes in learned behavior material were monitored every 2 hours in humans who had received DOM. Doses of 2.7 or 3.3mg were determined

to be the minimal dose. No perceptual or physiological changes were found at low doses, but were observed at doses greater than 5mg. A chimpanzee was given 5 or 10mg of DOM per os, and in 7 performance measurements a dose response relationship was manifested. At 10mg all perceptual discriminations, auditory as well as visual, and gross sensory motor functioning were affected in accuracy as well as time. Results with a 5mg dose suggest that fine perceptual discriminations can be affected while gross sensory motor functioning is unimpaired. This is in accordance with human experience, both experimental and street use. Residual effects after 24 hours seem to be negligible or nonexistent.

46200
AUTHORS: McIsaac, William Mallinson; Harris, Robert T.; Ho, Beng T.
TITLE: The indole hallucinogens.
SOURCE: In: Harris, R., Drug dependence.
SOURCEID: Austin, University of Texas Press, 1970. 342 p. (p. 41-54).

The chemical properties of indole derivatives which are hallucinogenic agents and their similarity to serotonin are discussed. Studies are reported of the structure action relationship of a series of tryptamines and beta-carbolines, using standard pharmacological and operant conditioning behavioral assays. The effects of O- and N-methylated substituted hydroxytryptamines on behavior maintained on positive reinforcement schedules were evaluated. O-methylation and N-dimethylation enhances activity, while N-acetylation seems to render the tryptamine inactive behaviorally. A comparison of 4- and 5-substituted tryptamines revealed a marked difference in the potencies of the 2 compounds, with psilocybin rendering an effect that could be considered a disruption of stimulus control. A number of beta-carbolines, which are potent inhibitors of monoamine oxidase (MAO), were studied to determine the degree to which this activity relates to changes in behavior. Results demonstrate that the behavioral effects of the compounds parallel their MAO inhibitory activity and that both functions are related to the degree of saturation present in the pyridine ring. It cannot be concluded that all beta-carbolines are hallucinogenics, but further study of the relationship of MAO activity and behavior is indicated. 33 references.

46313
AUTHORS: Wittenborn, J. R.
TITLE: Stress responses among normals.
SOURCE: In: Wittenborn, J., The response to meprobamate -- a predictive analysis.
SOURCEID: New York, Raven Press, 1970. 113 p. (p. 27-32).

The effects of meprobamate on stress responses in normal human subjects are reviewed. The published reports explore every aspect of cognitive and perceptual - motor performance, and the consequences of meprobamate on normal performance appear to be of little practical significance, particularly at dosages within the range of recommended therapeutic use. In some studies slowing or impairment was observed, but it appears to be consistent with the mildly sedating effect of meprobamate and is of little theoretical interest or practical consequence. Of greater interest is the fact that some enhancements of performance have been observed in stress - like situations where the ameliorating, therapeutic effects of meprobamate may be construed as protecting the subject from stress or distracting influences. The possibility that meprobamate may protect the normal subject fromsituational stress or circumstances which could detract from his performance is discussed.

46430
AUTHORS: no author.
TITLE: Marijuana.
SOURCE: Medical Letter on Drugs and Therapeutics.
SOURCEID: 12(8):1-3, 1970.

A brief background consideration of marihuana is given. The pharmacologic activity of Cannabis sativa results mainly from the tetrahydrocannabinol (THC) content of its flowering tops and upper leaves. The THC content may vary from near zero to 2% or more, depending upon the variety, the soil, climatic conditions, whether the plant is wild or cultivated, and the time of harvesting. Hashish, the brown resin collected from the tops and leaves of high quality marihuana, is far more potent that the plant parts. When marihuana is smoked, maximum effect is obtained with deep inhalation and retention of the smoke as long as possible. Time perception may be altered. Dysphoria occurs occasionally, though a feeling of relaxation or euphoria is more common. Most persons who use marihuana in moderation for a time are unlikely to suffer any lasting harmful effects. The effects of long-term use are not known.

46729
AUTHORS: Cohen, Sidney.
TITLE: The mind nobody knows.
SOURCE: In: Cohen, S., The beyond within: the LSD story.
SOURCEID: 2nd ed. New York, Atheneum, 1970. 312 p. (p. 64-82).

The argument is advanced that our future evolution lies as much in our minds as in our genes, that the vortex of unsanity must be studiously approached and tapped, and that the hallucinogens represent 1 approach to this problem. The nature of the thinking process under lysergic acid diethylamide (LSD) is examined in detail. Single thoughts branch rapidly into highly complicated ideational structures probably caused by a flood of associations ordinarily suppressed. The quality of thought is modified, with ideas becoming visible and acquiring an emotional component. Memory is selectively stimulated or impaired. Dreams and hallucinations were previously thought to be visitations from the spirit world, celestial or satanic in origin. We must establish a frame of reference to view the LSD induced hallucinations, as well as those deriving from schizophrenia, head injuries, fevers, and drugs, as the process of expanding our knowledge of the human mind and exploring the limits of the senses and psychic boundaries. Comments are included on the effect of LSD on the creative process. 3 references.

42521
AUTHORS: McDowell, Fletcher H.; Lee, John E.
TITLE: Levodopa, Parkinson's disease, and hypotension.
SOURCE: Annals of Internal Medicine.
SOURCEID: 72(5):751-752, 1970.

In a series of 100 patients with Parkinson's disease treated with levodopa, 25 developed significant orthostatic hypotension which was not dose - related. It usually appeared early in treatment and disappeared in most patients despite continuing treatment. Of the 25 patients, 20 no longer have orthostatic hypotension. Some of the possible explanations for the production of orthostatic hypotension by levodopa include impairment of carotid and aortic baroreceptor function, impaired catecholamine function and abnormalities of renin and aldosterone action. When dopamine is applied to the eye in eye drops, there is pupillary dilation, which can be blocked by guanethidine but subsequently reversed by phenylephrine eye drops. The most probable explanation of the mydriatic action of dopamine is its effect on sympathetic nerve endings to release noradrenaline. Other possible explanations of orthostatic hypotension related to catecholamines include the action of dopamine as a false transmitter and its action as an inhibitor of tyrosine hydroxylase. Levodopa has also been shown to reduce renin to undetectable levels, which may also be a basis for its orthostatic hypotensive effect. 7 references.

42655
AUTHORS: Castleman, Benjamin; McNeely, Betty U.
DESIG: Eds.
TITLE: Case records of the Massachusetts General Hospital: Case 20-1970.
SOURCE: New England Journal of Medicine.
SOURCEID: 282(19):1087-1096, 1970.

A case report is presented of a 22-year-old woman who was believed to have attempted suicide by taking an overdose of barbiturates. She vomited and possibly aspirated. She recovered consciousness after 72 hours but died on the 21st hospital day. Despite intensive orthodox treatment and one unusual therapeutic endeavor, the administration of nebulized surfactant, she remained in respiratory failure. The reasons for the patient's death were discussed. The clinical diagnosis was aspiration pneumonia secondary to barbiturate intoxication, with superimposed oxygen toxicity, staphylococcal pneumonia and terminal septicemia. The anatomical diagnosis was barbiturate intoxication, pulmonary interstitial fibrosis and hyaline membrane due to oxygen toxicity, ventilator cuff necrosis of the trachea, innominate vein thrombosis (bilateral), tricuspid valve endocarditis, pulmonary emboli and infarcts, and hemorrhagic cerebral infarcts. 31 references.

42687
AUTHORS: Adlerfligel; Govaerts, A.
TRTITLE: /Considerations of some side effects of drugs. (A study bearing on 11,410 calls received by the Belgian anti-poison center)./
TITLE: Considerations sur quelques effets secondaires des medicaments. (Etude portant sur 11,410 appels recus au Centre belge anti-poisons).
SOURCE: Bulletin de Medecine Legale et de Toxicologie Medicale (Lyons).
SOURCEID: 13(1):34-41, 1970.

The side-effects of various drugs, evaluated from the information given in calls for first-aid, are enumerated. These calls totalled 11410 and were directed to the Belgian Antitoxicity Center, and do not represent exact dosages (often guessed at). Of the neuroleptics, Haloperidol side-effects were symptomatic of

extrapyramidal disorders and spasms; the phenothiazines induced a hypertonic symptomatology of the extrapyramidal type. Those most frequently referred to were perphenazine, triethylperazine and periciazine. The analgesics induced itching, vertigo and nausea. The antibiotics (penicillin) produced allergic reactions (urticaria, itching). Tranquilizers and hypnotics (methaqualone, chloralose), anthelmintics, anticholinergics, vitamins, anticonvulsants and hormones are listed with their various side-effects.

42699
AUTHORS: Crane, George E.
TITLE: High doses of trifluperazine and tardive dyskinesia.
SOURCE: Archives of Neurology.
SOURCEID: 22(2):176-180, 1970.

A study of the effects of various dose levels of trifluperazine (Stelazine) in causing tardive dyskinesia is presented. Requirements for the inclusion of patients into this study were: a diagnosis of schizophrenia, age between 18 and 56, a minimum of 2 years continuous hospitalization, and absence of gross neurological or other physical disorders. Subjects were subdivided into patients under and over 40 years of age, patients hospitalized under and over 10 years, and by sex. Patients were then randomly assigned to drug regimens of 80mg and 16mg of trifluperazine and placebo for 6 months. During the subsequent 6 months, the patients received routine care at the discretion of the physician. There was a larger percentage of dyskinetic patients in the high dose sample although the difference was not statistically different. Following termination of the drug, dyskinesia increased in the high dose group, remained stationary in the low group and decreased in the placebo group. Thus, the difference between the high group and the other groups became statistically different. Results were compared to a previous study using chlorpromazine. The most important finding was that there was a high incidence of dyskinesia in chronic schizophrenic patients 40-years-old and over receiving large doses of the 2 neuroleptics. 8 references.

44134
AUTHORS: Bauer, Gunther.
TRTITLE: /Hashish and its effects./
TITLE: Haschisch und seine Wirkungen.
SOURCE: Polizei (Cologne).
SOURCEID: 61(3):121-124, 89-91, 1970.

This article on cannabis presents material on the chemistry of hashish preparation, pharmacology, the hallucinogenic experience, aggressive behavior or apathy induced by abuse of the substance, personality breakdown, danger of addiction, user motivation, and social questions. Public instruction should be instituted through working teams representing the schools, youth organization, social centers, etc. Discussion with young people is often difficult and an approach through warning slogans should be avoided. 14 references.

46205
AUTHORS: Essig, Carl.
TITLE: Barbiturate dependence.
SOURCE: In: Harris, R., Drug dependence.
SOURCEID: Austin, University of Texas Press, 1970. 342 p. (p. 129-140).

Barbiturate dependence is discussed. A group of newer nonbarbiturate sedative drugs that can produce states of intoxication and physical dependence similar to those induced by the barbiturates are also included in the study. The medical aspects of barbiturate intoxication and abstinence syndromes are covered, as well as treatment during withdrawal. 29 references.

46734
AUTHORS: Cohen, Sidney.
TITLE: The dangers to the patient -- and the therapist.
SOURCE: In: Cohen, S., The beyond within: the LSD story.
SOURCEID: 2nd ed. New York, Atheneum. 1970. 312 p. (p. 208-228).

The physical effects, side-effects, unusual effects, and addiction possibilities of lysergic acid diethylamide (LSD) are discussed on the basis of European and U. S. research. Data from 44 investigators dealing with 25000 administrations of LSD to 5000 people were received. The increasingly widespread use of hallucinogens by nonmedical groups for nonmedical purposes is described, with some ugly examples of the results. The marked tendency of a substantial minority of therapists dispensing the drug to demonstrate psychic disturbances is attributed to individual instability, latent notions of omniscience, and heavy consumption of the drugs themselves. An argument is advanced for strict controls of the hallucinogens to prevent adverse overreaction by the public. The question is posed as to whether chemically induced self-transcendence, ecstasy, and ego dissolution should be available to all who seek it, as Timothy Leary and his International Foundation for Internal Freedom (IFIF) have argued. A brief review of IFIF research with convicts is given, together with criticism of its methodology.

46735
AUTHORS: Cohen, Sidney.
TITLE: War without death.
SOURCE: In: Cohen, S., The beyond within: the LSD story.
SOURCEID: 2nd ed. New York, Atheneum, 1970. 312 p. (p. 229-237).

The use of hallucinogens for psychochemical warfare is discussed in detail; stockpiling, methods of delivery, and the stated premises of the military concerning such warfare are outlined. The actual results likely to occur in a city thus assaulted are covered in detail and found to be far from humane. The use of psychochemicals to interrogate special prisoners or to incapacitate decision makers is also considered to be counterproductive. 1 reference.

46558
AUTHORS: Hollister, Leo E.
TITLE: Methodological considerations in evaluating antianxiety drugs.
SOURCE: Journal of Clinical Pharmacology.
SOURCEID: 10(1):12-18, 1970.

A review is presented of methodological considerations in the measurement of anxiety and the evaluation of antianxiety drugs. Several methods of evaluating anxiety are discussed. Concepts of anxiety and the rating of anxiety by means of various tests and interviews are outlined. Experimental anxiety and antianxiety drugs are also considered. The efficacy, degree of sedation, and physiological relevance of various antianxiety drugs are discussed. 18 references.

43270
AUTHORS: Loeb, Michel; Alluisi, Earl A.
TITLE: Influence of display, task, and organismic variables on indices of monitoring behavior.
SOURCE: Acta Psychologica (Amsterdam).
SOURCEID: 33:343-366, 1970.

The effects of a number of variables known to influence monitoring behavior are reviewed. These variables are of 3 main types. Display variables include temporal factors, spatial factors, and signal conspicuity (which denotes the complex of conditions that vary the noticeability of the signal). The second category covers task variables, including signal - response compatibility, additional task loadings, and environmental factors, such as noise and heat. Organismic variables comprise the third category and include drug effects, factors related to sleep, individual differences, knowledge of results, monetary pay-off, and other interpersonal effects. The principal models for describing monitoring behavior are considered in light of the above variables. These theories are Pavlovian inhibition, expectancy hypothesis, arousal theory, signal detection theory, observing response concept, neurological hypotheses, and filter theory. It is suggested that all have merit in explaining some of the data, but none satisfactorily explains all. 110 references. (author abstract modified)

45515
AUTHORS: Tart, Charles T.
TITLE: Marihuana intoxication: common experiences.
SOURCE: Nature (London).
SOURCEID: 226(5247):701-704, 1970.

Traditional laboratory settings tend to provide limited information on the actual effects of marihuana intoxication because the situation inhibits many important manifestations of the subjects. For the benefit of future investigations, a questionnaire designed todetermine the most common effects of drug intoxication was distributed by students to seasoned marihauna users to maintain anonymity. Of the 750 questionnaires sent out, 153 were returned. The most common effects of marihuana were defined as those rated as occurring "sometimes", "very often" or "usually" by 50% of the respondents and are listed. Sensory perception and imagery are usually stronger, and great changes in perception, understanding, memory, emotion and sense of identity are noted. Although the validity of the descriptions cannot be proved, there is at least a great deal of agreement among the respondents. Nearly all the common effects were described as emotionally pleasing or cognitively interesting, but it should be remembered that negative effects are probably underrepresented. 11 references.

46136
AUTHORS: Ismail, A. A.; Gouda, M. Wafik; Motawi, M. M.
TITLE: Micellar solubilization of barbiturates I: solubilities of certain barbiturates in polysorbates of varying hydrophobic chain length.
SOURCE: Journal of Pharmaceutical Sciences.
SOURCEID: 59(2):220-224, 1970.

The effect of the hydrophobic chain length of the nonionic surfactants, polysorbates, on the degree of solubilization of a series of 5,5-disubstituted barbituric acid derivatives was studied. The solubilities were found to increase due to the formation of larger micelles as the hydrophobic chain length increases. A pseudo 2 phase model, according to which the drug molecule is partitioned between an aqueous phase and a micellar phase, was selected to determine the effect of the chemical structure of the solubilizate on the degree of solubilization. The number of carbon atoms of the substituents on the 5-position, as well as their inductive effects,

was found to determine the extent of solubilization. The order of solubilization of the drugs compared favorably with the order of their distribution coefficients between 1-octanol and water. 20 references. (author abstract modified)

46185
AUTHORS: Karnick, C. R.; Saxena, M. D.
TITLE: Datura Linn. -- the famous narcotic from the East -- a review.
SOURCE: Quarterly Journal of Crude Drug Research (Amsterdam).
SOURCEID: 10(1):1493-1516, 1970.

The recent literature on the genus Datura is reviewed. A considerable number of investigations had been conducted since Blakeslee's monumental publication (1959) on the genetic aspects of the genus Datura. New data has been brought to light from the various studies of tissue culture, physiology, pharmacology, toxicity, biosynthesis, and phytochemistry. All aspects of the research on Datura since 1959 are reviewed. 190 references. (author abstract modified)

46194
AUTHORS: Harris, Robert T.; McIsaac, William Mallinson; Schuster, Charles Robert, Jr.
DESIG: Eds.
TITLE: Drug dependence.
SOURCEID: Austin, University of Texas Press, 1970. 342 p. $10.00.

The proceedings are presented of the 2nd international symposium sponsored by the Texas Research Institute of Mental Sciences to discuss problems of drug dependence and abuse. Papers cover the biological, pharmacological, behavioral, social, and legal aspects of drug dependence. Five papers are devoted to therapeutic programs for drug dependence. The final paper discusses drug addiction in Mexico. 435 references.

46311
AUTHORS: Wittenborn, J. R.
TITLE: The response to meprobamate -- a predictive analysis.
SOURCEID: New York, Raven Press, 1970. 113 p. $6.75.

A predictive analysis is presented of the response to meprobamate. Attempts are made to conceptualize the effect of this psychotropic drug in terms which can evenutally be applied to the anticipation of the response of the individual patient. Only controlled studies of behavioral criteria were examined. The survey sought predictive patterns and makes no claim to be exhaustive. The general approach comprised 3 phases: the search for consistencies in the published literature, an attempt to conceptualize whatever consistencies emerged in the course of the 1st phase, and a review of all available reports of controlled clinical studies with the explicit purpose of determining which of the predictive deductions or hypotheses were consistent with the results of each of the investigations. 130 references.

46314
AUTHORS: Wittenborn, J. R.
TITLE: A pragmatic theory of meprobamate effects.
SOURCE: In: Wittenborn, J., The response to meprobamate --a predictive analysis.
SOURCEID: New York, Raven Press, 1970. 113 p. (p. 33-38).

A pragmatic theory of meprobamate effects is presented. Meprobamate has long been known as an interneuronal blocking agent with anticonvulsant properties, as a central relaxant, and as a mild tranquilizer which may be safely used in the amelioration of anxiety and tension. Certain questions relevant to its optimal use remain

unanswered. Its clinical effects have never been conceptualized in such a way as to permit a prediction of those particular individuals who will respond with the desired symptomatic modifications and of those individuals whose symptoms may remain relatively unaffected. The responses of laboratory animals, normal human subjects, medical patients, and psychiatric and behavioral patients to meprobamate have been described. It was hoped that this could provide an incisive, behaviorally pertinent conceptualization of the chemical effects of meprobamate, inferences which could be used as the basis for deducing the probable consequences of meprobamate medication in various types of situations. Such deductions would provide a basis for the predictive identification of those individuals who might or might not be expected to respond to meprobamate in the desired manner. Several working generalizationsapplicable to the clinical use of meprobamate are presented. Specific deductions which may be made when these generalizations are applied to clinical problems are outlined.

46736
AUTHORS: Cohen, Sidney.
TRTITLE: /Uses and misuses of lysergic acid diethylamide./
TITLE: Postview.
SOURCE: In: Cohen, S., The beyond within: the LSD story.
SOURCEID: 2nd ed. New York, Atheneum, 1970. 312 p. (p. 238-245).

An overview is presented of the use and misuse of lysergic acid diethylamide (LSD). The need for more information on the intrastructure of the mind, our drives, impulses, and emotions is urgent. The precise role of LSD and other hallucinogens as an adjunct to psychotherapy cannot be predicted from an analysis of the present situation. They offer great promise as a laboratory aid to the study of both the normal and abnormal activities of the mind. Their use for mysticomimetic experiences or social revolt may bring repressive legislation which will further inhibit scientific experimentation. There are no good or bad drugs, but only good or bad uses of drugs. 1 reference.

47681
AUTHORS: Peterson, Ernest.
TITLE: Psychopharmacology: introduction to general psychology: a self-selection textbook.
SOURCEID: Dubuque, Iowa, Wm. C. Brown, 1970. 46 p. 85 cents.

The principles and problems of the field of psychopharmacology are introduced. Psychoactive drugs are classified in 5 groups: tranquilizers, stimulants and antidepressants, sedatives and hypnotics, psychotomimetics or hallucinogenics, and the biogenic amines. Factors which are discussed are the modification of drug effects by the nature of the drug itself and its administration, the environment, genetic and physiological characteristics of the organism, and behavioral and psychological characteristics of the organism. Problems involved in research design in psychopharmacology are presented, with emphasis on use of the placebo. The clinical value of various drugs has been demonstrated in studies using double-blind techniques, control groups, and quantitative measurement, with rating scales and psychological tests. Tests of individual psychomotor performance are often of value in determining the differential effects of drugs. Studies employing animals in conditioned response situations have been particularly important. Neurophysiological and electrophysiological techniques have recently undergone rapid advancement and have contributed to the understanding of basic drug mechanisms. Finally, the various pharmacological methods by which the site and mode of drug action is determined are discussed. These include microinjection and the use of drugs labeled with radioactive isotopes. 136 references.

51111
AUTHORS: Elliott, Henry W.; Cutting, Windsor C.; Dreisbach, Robert H.

DESIG: Eds.
TITLE: Annual review of pharmacology.
SOURCEID: Palo Alto, Calif., Annual Reviews, 1970. 505 p. Vol. 10.

A review is presented of new concepts in pharmacology, including: pharmacology and medicine; receptor mechanisms; cyclic AMP and drug action; specific irreversible enzyme inhibitors; relationships between stereostructure and pharmacological activities; the metabolic alteration of drugs; species differences in drug metabolism; antibiotic interaction with model membranes; pharmacology of viruses; nonsteroid antiinflammatory agents; inhibitors of adrenal steroid biosynthesis; endocrine hormones; antifertility agents; developmental pharmacology; regulation of norepinephrine biosynthesis; cardiac pharmacology; psychopharmacology; cellular aspects of invertebrate neuropharmacology; persistent pesticides; toxicity of ozone, oxygen, and radiation; aerospace problems in pharmacology and toxicology; challenges in drug evaluation in man; and l-asparaginase and l-asparagine metabolism. Each topic is discussed extensively. 3227 references.

51112
AUTHORS: Kumagai, Hiroshi.
TITLE: Pharmacology and medicine.
SOURCE: In: Elliott, H., Annual review of pharmacology.
SOURCEID: Palo Alto, Calif., Annual Reviews, 1970. 505 p. Vol. 10. (p. 1-6).

The establishment and independence of pharmacology in Japan are discussed. The Department of Pharmacology of the Faculty of Medicine at the University of Tokyo has served as a source of training of professors of pharmacology for other medical colleges and medical faculties. The Japanese Pharmacological Society was established in 1927. Special efforts in pharmacology were 1st directed to the teaching of biology to students of chemistry rather than biological sciences. Pharmacology by definition is the study of the response of living matter to substances (chemical or physical) administered, and belongs to experimental biology and experimental medicine. Basic studies being conducted on muscle contraction have shown the role of calcium as the basis of the pharmacological action of such drugs as caffeine.

51113
AUTHORS: Burgen, A. S. V.
TITLE: Receptor mechanisms.
SOURCE: In: Elliott, H., Annual review of pharmacology.
SOURCEID: Palo Alto, Calif., Annual Reviews, 1970. 505 p. Vol. 10. (p. 7-18).

Problems of receptor pharmacology are reviewed. Closer definition of the sites of drug action is recommended. Improved knowledge of the structure of the binding sites and an understanding of the configuration of the drug in its bound state are also needed. Research is needed to determine how the receptor events are translated into physiological events. Problems related to the cholinoreceptor are reviewed. Topics covered include the structure and conformation of drugs, discrimination of receptor sites, uptake processes, the relationship of acetylcholinesterase to the cholinoreceptors, and chemical modification of receptors. 121 references.

51115
AUTHORS: Baker, B. R.
TITLE: Specific irreversible enzyme inhibitors.
SOURCE: In: Elliott, H., Annual review of pharmacology.
SOURCEID: Palo Alto, Calif., Annual Reviews, 1970. 505 p. Vol. 10 (p. 35-50).

A review is presented of the literature on specific irreversible

enzyme inhibitors. The study of enzyme inhibition has its roots in 2 lines of scientific pursuit: the study of enzyme kinetics not directly concerned with pharmacology and the study of the mechanism of action of pharmacologically active compounds at the molecular level of the enzyme. Reversible and irreversible inhibitors are discussed. An irreversible inhibitor no longer dissociates from the enzyme and the enzyme reaction is slowed an amount dependent upon only enzyme and inhibitor concentrations, but is independent of substrate concentration. There are 2 types of irreversible inhibitors. The 1st is so strongly complexed to the enzyme that it fails to dissociate from the enzyme under physiological conditions but can be dissociated by dialysis or by chromatography. The 2nd type of irreversible inhibition is due to the formation of a covalent bond between the enzyme and the inhibitor; if the new covalent bond stops conversion of substrate to product, the enzyme has been inactivated irreversibly. Irreversible enzyme inhibitors discussed include dihydrofolate reductase, anabolic and catabolic enzymes for nucleosides, and serine type proteases. 104 references. (author abstract modified)

51116
AUTHORS: Portoghese, Philip S.
TITLE: Relationships between stereostructure and pharmacological activities.
SOURCE: In: Elliott, H., Annual review of pharmacology.
SOURCEID: Palo Alto, Calif., Annual Reviews, 1970. 505 p. Vol. 10. (p. 51-76).

The role of stereochemical factors in the action of drugs on excitable tissue is discussed. The material covered deals with steric factors arising from asymmetric centers and from conformational isomerism in molecules that exert their primary action at cholinergic, adrenergic, analgestic, histaminic, and serotonin receptors. A highly selective interpretative appraisal of the present status of the subject is presented. The stereoselectivity of drugs with enzymes is not discussed. 162 references. (author abstract modified)